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C07D277/48, C07D417/12

(54) **7-Acylamino-3-vinylcephalosporanic acid derivatives, processes for their preparation, pharmaceutical compositions containing them; their starting compounds and their preparation.**

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GB-A-1 342 241
GB-A-1 399 088

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Description

The present invention relates to novel 7-acylamino-3-vinylcephalosporanic acid derivatives and pharmaceutically acceptable salts thereof.

More particularly it relates to novel 7-aceylamino-3-vinylcephalosporanic acid derivatives and pharmaceutically acceptable salts thereof, which have antimicrobial activity, to processes for the preparation thereof, to a pharmaceutical composition comprising the same, and to such compounds for use in the treatment of infectious diseases in human beings and animals.

7-Acylamino-3-vinyl-ceph-3-em-carboxylic acids and esters thereof are known from GB—A—1 342 241. GB—A—1 399 088 relates to similar compounds where the acylamino group is substituted by the oxyamino group.

EP—A—0 123 024 describes starting compounds which can be used for the preparation of the present compounds.

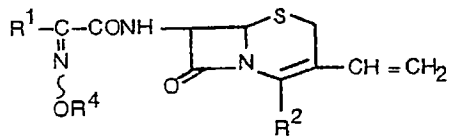
One object of the present invention is to provide novel 7-acylamino-3-vinylcephalosporanic acid derivatives and their pharmaceutically acceptable salts, which are highly active against a number of pathogenic microorganisms and are useful as antimicrobial agents, especially for oral administration.

Another object of the present invention is to provide processes for the preparation of novel 7-acylamino-3-vinylcephalosporanic acid derivatives and pharmaceutically acceptable salts thereof.

A further object of the present invention is to provide a pharmaceutical composition comprising, as active ingredients, said 7-acylamino-3-vinylcephalosporanic acid derivatives and pharmaceutically acceptable salts thereof.

Still further object of the present invention is to provide said 7-acylamino-3-vinylcephalosporanic acid derivatives and pharmaceutically acceptable salts thereof for use in the tratment of infectious diseases by pathogenic microorganisms in human being and animals.

The object 7-acylamino-3-vinylcephalosporanic acid derivatives are novel and can be represented by the following general formula:



in which

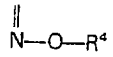
R^1 is aminothiazolyl which may have halogen, aminothiadiazolyl, protected aminothiazolyl which may have halogen or protected aminothiadiazolyl,

R^2 is carboxy or a protected carboxy group, and

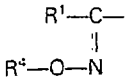
R^4 is hydrogen, cyclo(C_3—C_7)alkenyl, C_2—C_7 alkynyl, C_2—C_7 alkenyl, C_2—C_7 alkenyl substituted by carboxy or a protected carboxy group, C_1—C_7 alkyl, or C_1—C_7 alkyl substituted by one or more substituent(s) selected from carboxy, a protected carboxy group, amino, a protected amino group, cyano, phosphono, a protected phosphono group and pyridyl.

In the object compounds (I) and the corresponding starting compounds (II) to (VI) in Processes 1, 5 and 7 mentioned below, it is to be understood that there may be one or more stereoisomeric pair(s) such as optical and geometrical isomers due to asymmetric carbon atom and double bond in those molecules and such isomers are also included within the scope of the present invention.

With regard to geometrical isomers in the object compounds and the starting compounds, it is to be noted that, for example, a partial structure of a group of the formula: $=C=N\sim OR^4$ includes syn isomer, anti isomer and a mixture thereof, and the syn isomer means one geometrical isomer having the partial structure represented by the following formula:



wherein R^1 and R^4 are each as defined above, and the anti isomer means the other geometrical isomer having the partial structure represented by the following formula:



wherein R^1 and R^4 are each as defined above.

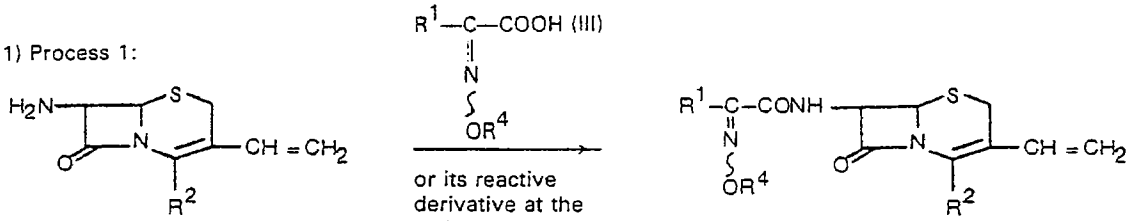
Regarding the other object and starting compounds as mentioned above, the syn isomer and the anti isomer can also be referred to the same geometrical isomers as illustrated for the compounds (I).

Suitable pharmaceutically acceptable salts of the object compounds (I) are conventional non-toxic salts and may include e.g. a salt with a base or an acid addition salt such as a salt with an inorganic base, for

example, an alkali metal salt (e.g. sodium salt, potassium salt), an alkaline earth metal salt (e.g. calcium salt, magnesium salt), an ammonium salt; a salt with an organic base, for example, an organic amine salt (e.g. triethylamine salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt); an inorganic acid addition salt (e.g. hydrochloride, hydrobromide, sulfate, phosphate); an organic carboxylic or sulfonic acid addition salt (e.g. formate, acetate, trifluoroacetate, maleate, tartrate, methanesulfonate, benzenesulfonate, p-toluenesulfonate); a salt with a basic or acidic amino acid (e.g. arginine, aspartic acid, glutamic acid); an intermolecular or intramolecular quaternary salt. The said intermolecular quaternary salt can be formed in case that R^4 in the compounds (I) is pyridyl, and suitable intermolecular quaternary salt may include e.g. 1-C_1—C_7 alkylpyridinium C_1—C_7 alkylsulfate (e.g. 1-methylpyridinium methylsulfate, 1-ethylpyridinium ethylsulfate) and 1-C_1—C_7 alkylpyridinium halide (e.g. 1-methylpyridinium iodide). The said intramolecular salt can be formed in case that R^4 in the compounds (I) is pyridyl and R^2 is carboxy, and suitable intramolecular salt may include e.g. 1-C_1—C_7 alkylpyridinium carboxylate (e.g. 1-methylpyridinium carboxylate, 1-ethylpyridinium carboxylate, 1-propylpyridinium carboxylate, 1-isopropylpyridinium carboxylate and 1-butylpyridinium carboxylate).

According to the present invention, the object compounds (I) and the pharmaceutically acceptable salts thereof can be prepared by the processes as illustrated by the following reaction schemes.

(1) Process 1:



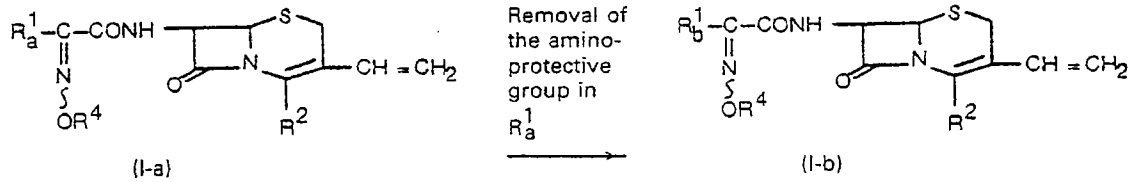
(II)

or its reactive derivative at the amino group or a salt thereof

(I)

or a salt thereof

(2) Process 2:



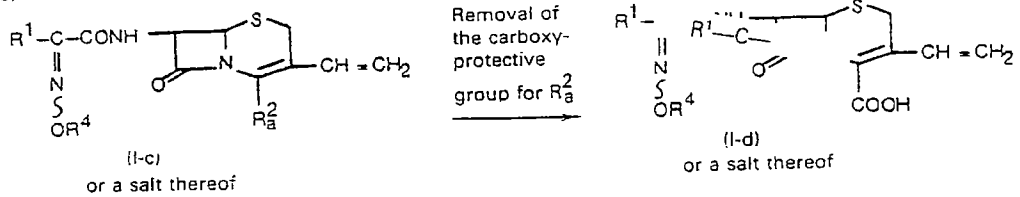
(I-a)

or a salt thereof

(I-b)

or a salt thereof

(3) Process 3:



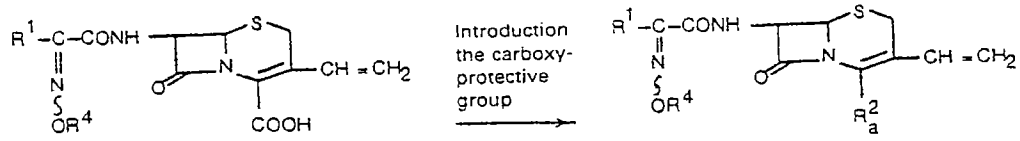
(I-c)

or a salt thereof

(I-d)

or a salt thereof

(4) Process 4:



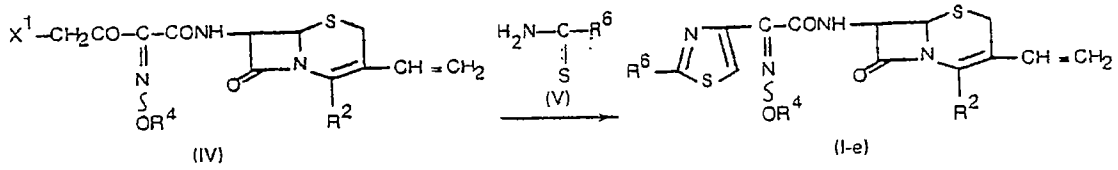
(I-d)

or a salt thereof

(I-c)

or a salt thereof

(5) Process 5:



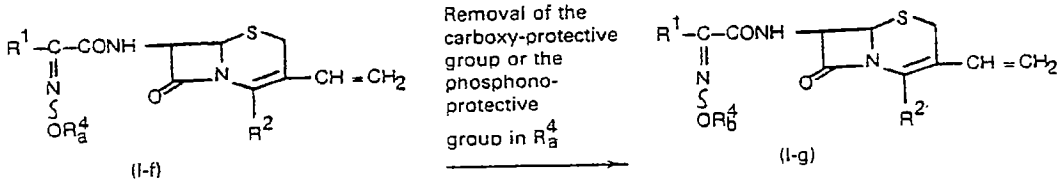
(IV)

or a salt thereof

(I-e)

or a salt thereof

(6) Process 6:



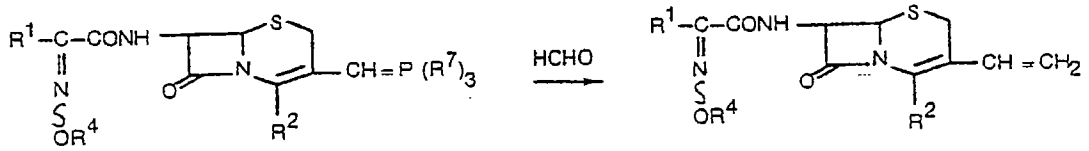
(I-f)

or a salt thereof

(I-g)

or a salt thereof

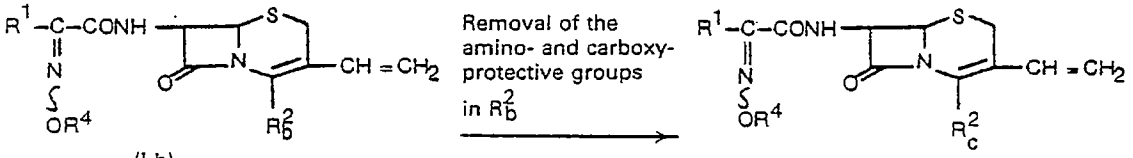
(7) Process 7:



or a salt thereof

or a salt thereof

(8) Process 8:



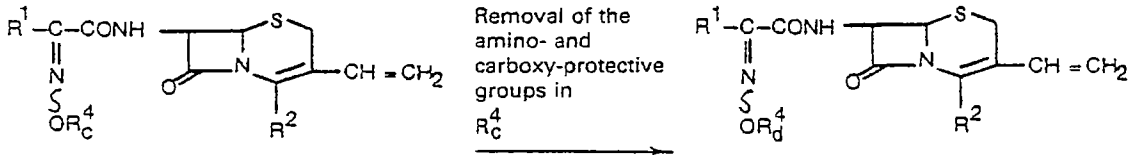
(I-h)

or a salt thereof

(I-i)

or a salt thereof

(9) Process 9:



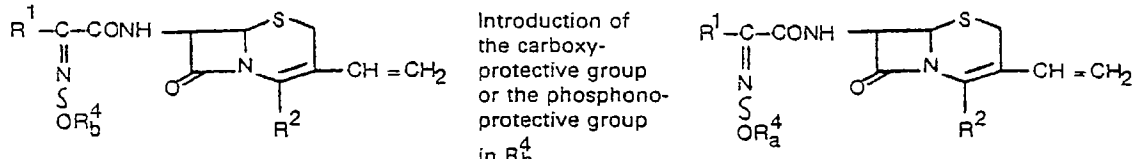
(I-j)

or a salt thereof

(I-k)

or a salt thereof

(10) Process 10:



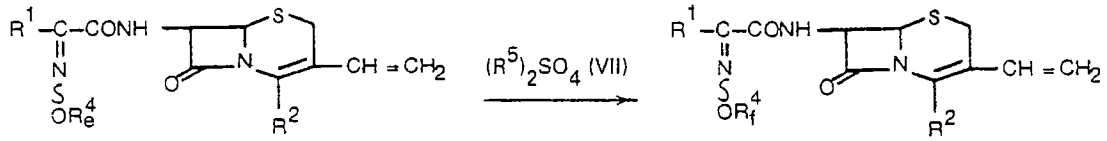
(I-g)

or a salt thereof

(I-f)

or a salt thereof

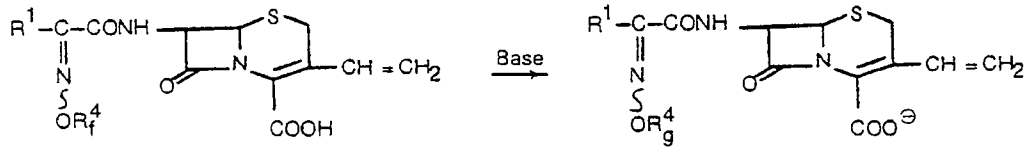
(11) Process 11:



(I-l) (I-m)

or a salt thereof or a salt thereof

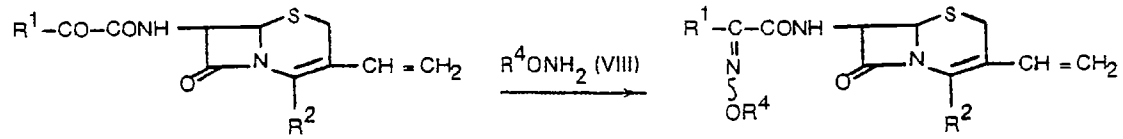
(12) Process 12:



(I-n) (I-o)

or a salt thereof or a salt thereof

(13) Process 13:



(I-r) (I)

or a salt thereof or a salt thereof

in which

R^1, R^2 and R^4 are each as defined above,

R^1_a is protected aminothiazolyl which may have halogen or protected aminothiadiazolyl,

R^1_b is aminothiazolyl which may have halogen or aminothiadiazolyl,

R^2_a is a protected carboxy group,

R^2_b is C_1—C_7 alkoxycarbonyl substitued by a protected amino and a protected carboxy groups,

R^2_c is C_1—C_7 alkoxycarbonyl substituted by amino and carboxy,

R^5 is C_1—C_7 alkyl,

R^6 is amino or a protected amino group,

R^7 is aryl,

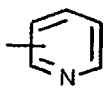
R^4_a is C_1—C_7 alkyl substituted by a protected carboxy group or a protected phosphono group, or C_2—C_7 alkenyl substituted by a protected carboxy group,

R^4_b is C_1—C_7 alkyl substituted by carboxy or phosphono, or C_2—C_7 alkenyl substituted by carboxy,

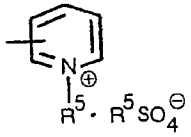
R^4_c is C_1—C_7 alkoxycarbonyl (C_1—C_7) alkyl substituted by a protected amino and a protected carboxy groups, or C_1—C_7 alkyl substituted by a protected amino and a protected carboxy groups,

R^4_d is C_1—C_7 alkoxycarbonyl(C_1—C_7)alkyl substituted by amino and carboxy, or C_1—C_7 alkyl substituted by amino and carboxy,

R^4_e is C_1—C_7 alkyl substituted by a group of the formula:

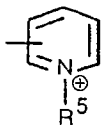


R^4_f is C_1—C_7 alkyl substituted by a group of the formula:



wherein R^5 is as defined above,

R^4_9 is C_1—C_7 alkyl substituted by a cation of the formula

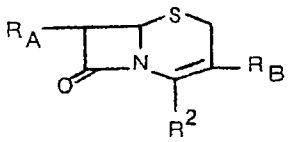


wherein R^5 is as defined above, and

X^1 is halogen.

Some of the starting compounds (II), (III), (IV), (VI) and (VIII) used in Processes 1, 5, 7 and 13 are new and can be represented by the following general formulae:

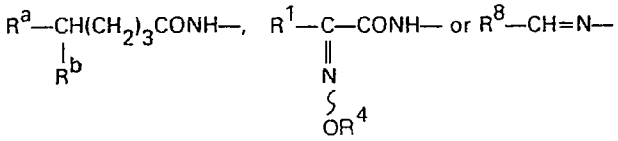
(1)



(Compound ①)

in which

R_A is a group of the formula:



wherein

R^8 is aryl,

R^a is a protected amino group,

R^b is a protected carboxy group, and

R^1 and R^4 are each as defined above,

R_B is a group of the formula:

$$—CH_2—X^2, —CH_2P^{\oplus}(R^7)_3 \cdot X^{3\ominus} \text{ or } —CH=P(R^7)_3$$

wherein

X^2 and X^3 are each halogen, and

R^7 is as defined above, and

R^2 is as defined above;

provided that, when R_A is a group of the formula: R^8—CH=N—, wherein R^8 is as defined above, then

R_B is a group of the formula:

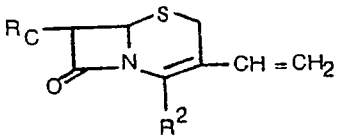
$$—CH_2P^{\oplus}(R^7)_3 \cdot X^{3\ominus} \text{ or } —CH=P(R^7)_3,$$

wherein

R^7 and X^3 are each as defined above,

or a salt thereof; and

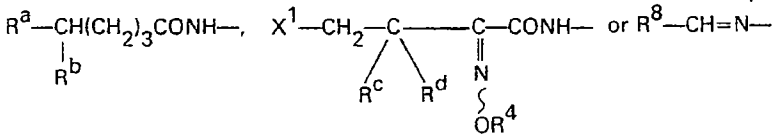
(2)



(Compound ②)

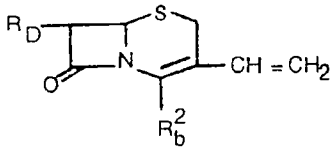
in which

R_C is amino or a group of the formula:



wherein
R^c and R^d are combined to form oxo or a protected oxo group, and
R^4, R^8, R^a, R^b and X^1 are each as defined above, and
R^2 is as defined above;
provided that, when R_c is amino, then R^2 is carboxy,
or a salt thereof; and

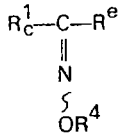
③



(Compound ③)

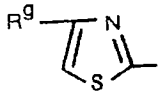
in which
R_D is amino or a protected amino group, and
R_b^2 is as defined above,
or a salt thereof; and

④



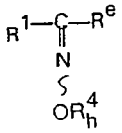
(Compound ④)

in which
R_c^1 is a group of the formula:



wherein
R^g is carboxy or a protected amino group,
R^e is carboxy or a protected carboxy group, and
R^4 is as defined above,
or a salt thereof; and

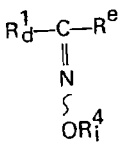
⑤



(Compound ⑤)

in which
R_h^4 is C_2—C_7 alkenyl substituted by carboxy or a protected carboxy group, C_1—C_7 alkyl substituted by a protected amino and a protected carboxy groups, C_1—C_7 alkyl substituted by a protected amino- and a protected carboxy-substituted-C_1—C_7 alkoxycarbonyl, or C_1—C_7 alkyl substituted by pyridyl, and
R^1 and R^e are each as defined above,
or a salt thereof; and

⑥



(Compound ⑥)

in which
R_d^1 is aminothiazolyl having halogen, protected aminothiazolyl having halogen,
R_i^4 is C_1—C_7 alkyl substitued by carboxy or a protected carboxy group, and
R^e is as defined above,
or a salt thereof; and

⑦ R^h—O—R_H^4 (Compound ⑦)

in which

R^h is amino or phthalimido, and

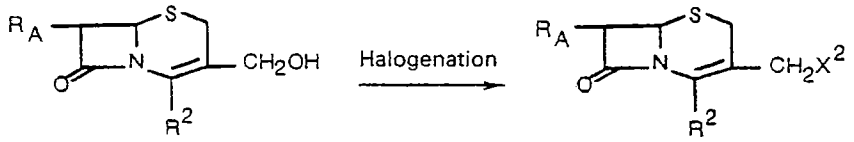
R^4_H is as defined above,

or a salt thereof.

Suitable salts of the starting compounds ① to ⑦ thus formulated may include the same ones as exemplified for the compounds (I).

The starting compounds ① to ⑦ and other starting compounds can be prepared, for example, from the known compounds by the methods in the following Processes ① to ⑩ or in a similar manner thereto or in a conventional manner.

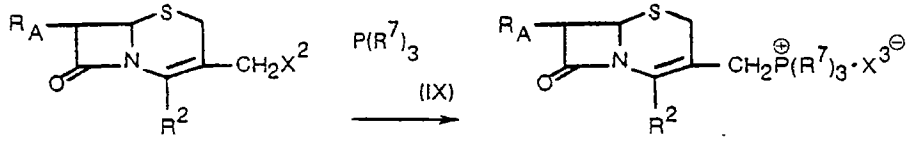
Process ①-(1):



(①-a) (①-b)

or a salt thereof or a salt thereof

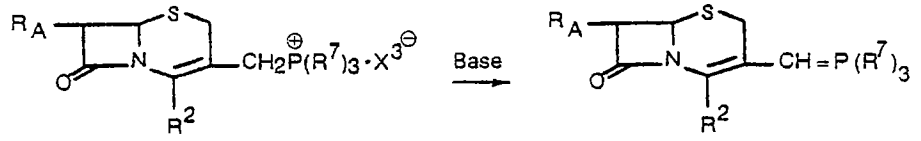
Process ①-(2):



(①-b) (①-c)

or a salt thereof or a salt thereof

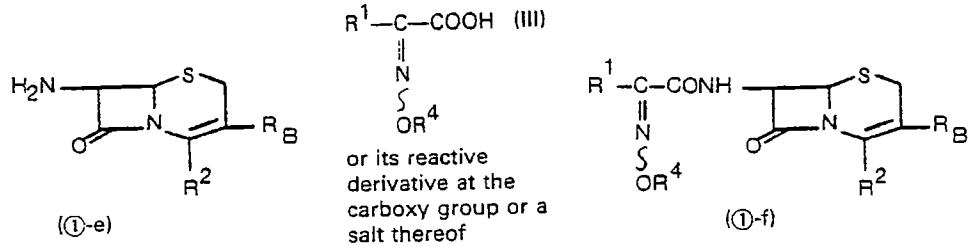
Process ①-(3):



(①-c) (①-d)

or a salt thereof or a salt thereof

Process ①-(4):



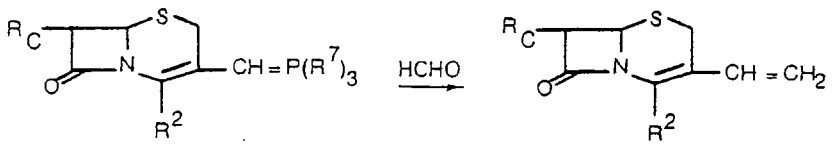
(①-e) (①-f)

or its reactive derivative at the amino group or a salt thereof

or its reactive derivative at the carboxy group or a salt thereof

or a salt thereof

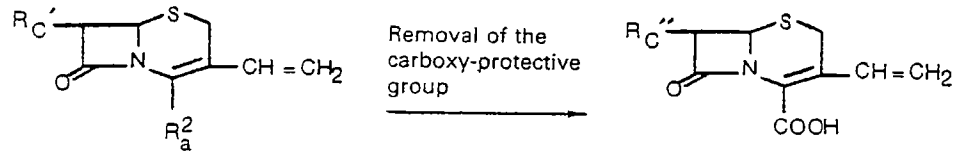
Process ②-(1):



(②-a) (②-b)

or a salt thereof or a salt thereof

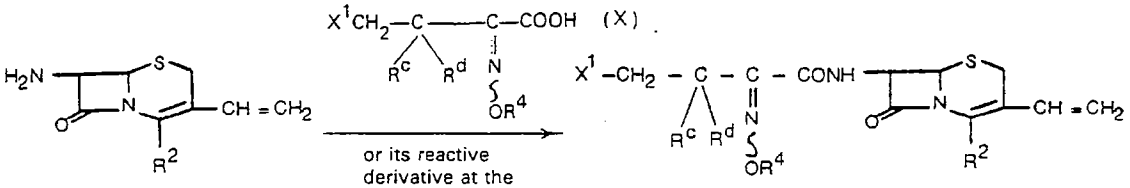
Process ②-(2):



(②-c) (②-d)

or a salt thereof or a salt thereof

Process ②-(3):

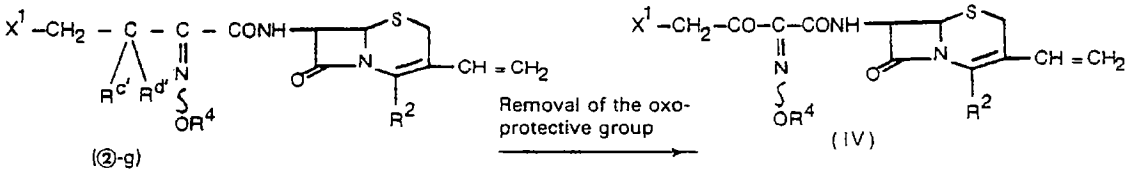


(②-e) (②-f)

or its reactive derivative at the carboxy group or a salt thereof

or a salt thereof

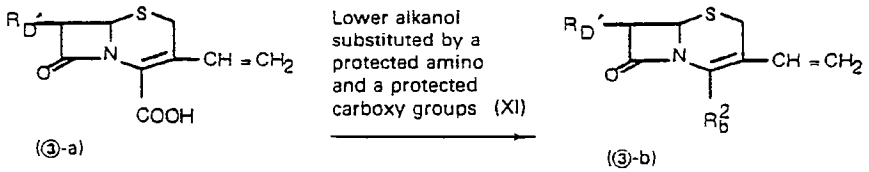
Process ②-(4):



(②-g) (IV)

or a salt thereof or a salt thereof

Process ③-(1):

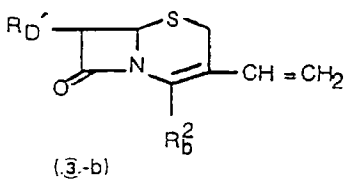


(③-a) (③-b)

or its reactive derivative at the carboxy group or a salt thereof

or a salt thereof

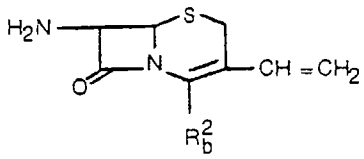
Process ③-(2):



(③-b)

or a salt thereof

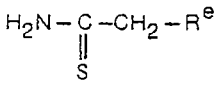
Removal of the amino-protective group



(③-c)

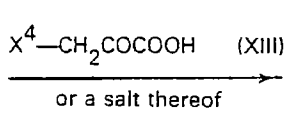
or a salt thereof

Process ④-(1):

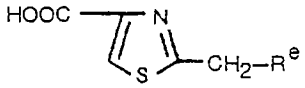


(④-e)

or a salt thereof



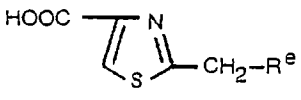
or a salt thereof



(④-f)

or a salt thereof

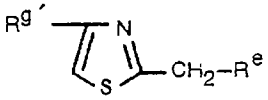
Process ④-(2):



(④-f)

or a salt thereof

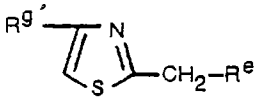
(i) Azidation
(ii) Thermal Degradation
(iii) Alcohol



(④-g)

or a salt thereof

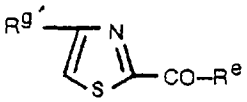
Process ④-(3):



(④-g)

or a salt thereof

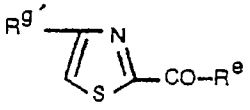
Oxidation



(④-h)

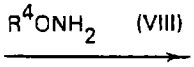
or a salt thereof

Process ④-(4):

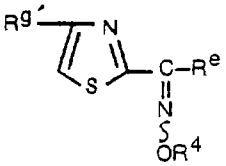


(④-h)

or a salt thereof



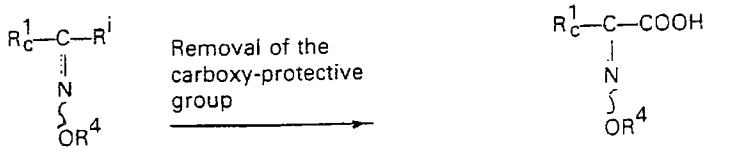
or a salt thereof



(④-i)

or a salt thereof

Process ④-(5):



(④-j)

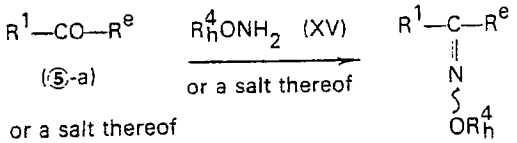
or a salt thereof

Removal of the carboxy-protective group

(④-k)

or a salt thereof

Process ⑤:



(⑤-a)

or a salt thereof

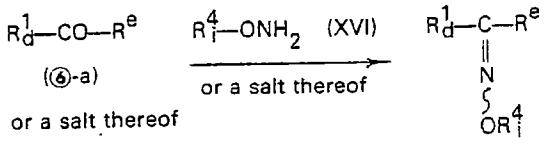
$R_h^4ONH_2$ (XV)

or a salt thereof

(⑤-b)

or a salt thereof

Process ⑥:



(⑥-a)

or a salt thereof

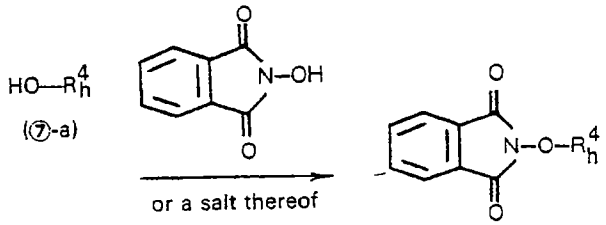
$R_i^4—ONH_2$ (XVI)

or a salt thereof

(⑥-b)

or a salt thereof

Process ⑦-(1):



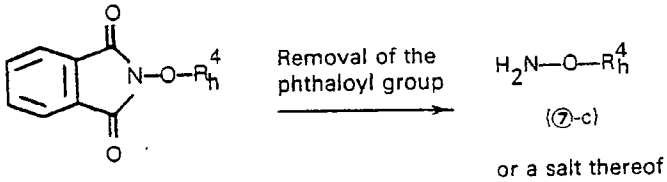
(⑦-a)

or a salt thereof

or a reactive derivative at the hydroxy group

(⑦-b)

Process ⑦-(2):



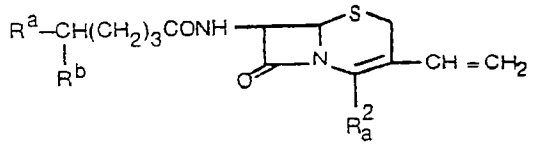
(⑦-b)

Removal of the phthaloyl group

(⑦-c)

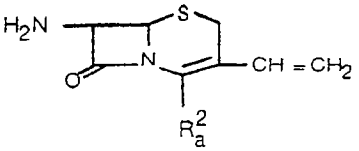
or a salt thereof

Process ⑧:



(⑧-a)

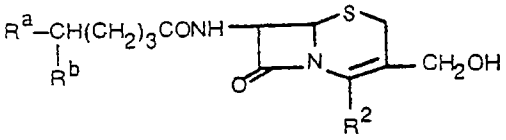
Removal of the acyl group



(⑨-b)

or a salt thereof

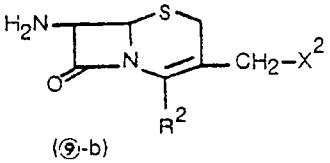
Process ⑨:



(⑨-a)

or a salt thereof

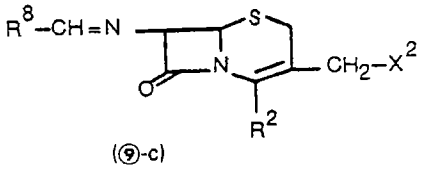
Removal of the acyl group (Step 1)



(⑨-b)

or a salt thereof

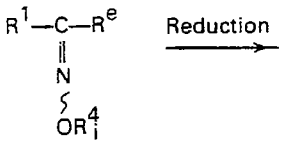
R^8—CHO (XVII) (Step 2)



(⑨-c)

or a salt thereof

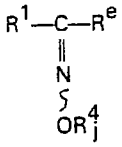
Process ⑩:



(⑩-a)

or a salt thereof

Reduction



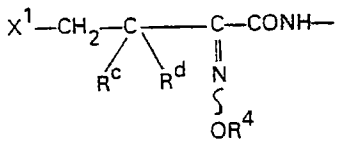
(⑩-b)

or a salt thereof

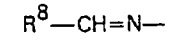
in which

R_A, R_B, R_C, R^1, R^1_c, R^1_d, R^2, R^2_a, R^2_b, R^4, R^4_h, R^4_i, R^7, R^8, R^a, R^b, R^c, R^d, R^e, X^1, X^2 and X^3 are each as defined above,

R^c_c is amino or a group of the formula:

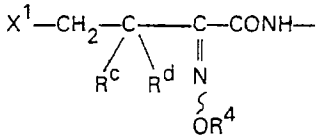


or



wherein R^8, R^c, R^d, R^4 and X^1 are each as defined above,

R_c' is amino or a group of the formula:



wherein R^c, R^d, R^4 and X^1 are each as defined above,

R_b' and $R^{g'}$ are each a protected amino group,

$R^{c'}$ and $R^{d'}$ are combined to form a protected oxo group,

R^1 is a protected carboxy group,

R_j^4 is C_2—C_7 alkenyl substituted by carboxy or a protected carboxy group, and

X^4 is halogen.

In the above and subsequent description of the present specification, suitable examples and illustration of the various definitions to be included within the scope thereof are explained in detail as follows.

Suitable "C_1—C_7 alkyl" group may include straight or branched one such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, isopentyl, neopentyl, hexyl and the like, in which the preferred one is C_1—C_4 alkyl.

Suitable "C_2—C_7 alkenyl" group may include straight or branched one such as vinyl, 1-propenyl, allyl, 1-(or 2- or 3-)butenyl, 1-(or 2- or 3- or 4-)pentenyl, 1-(or 2- or 3- or 4- or 5-)hexenyl and 2-methyl-2-propenyl, in which the preferred one is C_2—C_5 alkenyl.

Suitable "C_2—C_7 alkynyl" group may include straight or branched one such as propargyl, 2-(or 3-)butynyl, 2-(or 3- or 4-)pentynyl and 2-(or 3- or 4- or 5-)hexynyl, in which the preferred one is C_2—C_5 alkynyl.

Suitable "cyclo(C_3—C_7)alkenyl" group may include e.g. cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl and cycloheptenyl, in which the preferred one is C_5—C_6 cycloalkenyl.

Suitable "protected amino" group may include an amino group substituted by a conventional amino-protective group which is used in penicillin and cephalosporin compounds, for example, acyl as mentioned below, ar(C_1—C_7)alkyl such as mono- (or di- or tri-)phenyl(C_1—C_7)alkyl (e.g. benzyl, benzhydryl, trityl), C_1—C_7 alkoxycarbonyl(C_1—C_7)alkylidene or its enamine tautomer (e.g. 1-methoxycarbonyl-1-propen-2-yl) and di(lower)alkylaminomethylene (e.g. dimethylaminomethylene).

Suitable "acyl" may include an aliphatic acyl, an aromatic acyl, a heterocyclic acyl and an aliphatic acyl substituted with aromatic or heterocyclic group(s).

The aliphatic acyl may include saturated or unsaturated, acyclic or cyclic ones, such as C_1—C_7 alkanoyl (e.g. formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, etc.), C_1—C_7 alkanesulfonyl (e.g. mesyl, ethanesulfonyl, propanesulfonyl), C_1—C_7 alkoxycarbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, tert-butoxycarbonyl), C_1—C_7 alkenoyl (e.g. acryloyl, methacryloyl, crotonoyl), (C_3—C_7)-cycloalkanecarbonyl (e.g. cyclohexanecarbonyl) and amidino.

The aromatic acyl may include e.g. aroyl (e.g. benzoyl, toluoyl, xyloyl) and arenesulfonyl (e.g. benzenesulfonyl, tosyl).

The heterocyclic acyl may include e.g. heterocyclecarbonyl (e.g. furoyl, thenoyl, nicotinoyl, isonicotinoyl, thiazolylcarbonyl, thiadiazolylcarbonyl and tetrazolylcarbonyl).

The aliphatic acyl substituted with aromatic group(s) may include e.g. ar(C_1—C_7)alkanoyl such as phenyl(C_1—C_7)alkanoyl (e.g. phenylacetyl, phenylpropionyl, phenylhexanoyl), ar(C_1—C_7)alkoxycarbonyl such as phenyl(C_1—C_7)alkoxycarbonyl (e.g. benzoyloxycarbonyl, phenethyloxycarbonyl) and phenoxy(C_1—C_7)alkanoyl (e.g phenoxyacetyl, phenoxypropionyl).

The aliphatic acyl substituted with heterocyclic group(s) may include e.g. thienylacetyl, imidazolylacetyl, furylacetyl, tetrazolylacetyl, thiazolylacetyl, thiadiazolylacetyl, thienylpropionyl and thiadiazolylpropionyl.

These acyl groups may be further substituted with one or more suitable substituents such as C_1—C_7 alkyl (e.g. methyl, ethyl, propyl, isopropyl, butyl, pentyl, hexyl), halogen (e.g. chlorine, bromine, iodine, fluorine), C_1—C_7 alkoxy (e.g methoxy, ethoxy, propoxy, isopropoxy, butoxy, pentyloxy, hexyloxy), C_1—C_7 alkylthio (e.g. methylthio, ethylthio, propylthio, isopropylthio, butylthio, pentylthio, hexylthio) and nitro, and preferably acyl having such substituent(s) may be e.g. mono (or di or tri)halo(C_1—C_7)alkanoyl (e.g. chloroacetyl, bromoacetyl, dichloroacetyl, trifluoroacetyl), mono (or di or tri)halo(C_1—C_7)alkoxycarbonyl (e.g. chloromethoxycarbonyl, dichloromethoxycarbonyl, 2,2,2-tri-chloroethoxycarbonyl), nitro (or halo or C_1—C_7 alkoxy)phenyl(C_1—C_7)alkoxycarbonyl (e.g. nitrobenzyloxycarbonyl, chlorobenzyloxycarbonyl, methoxybenzyloxycarbonyl).

Suitable "protected carboxy" group may include an esterified carboxy group which is conventionally used in penicillin or cephalosporin compounds at their 3rd or 4th position thereof.

Suitable "ester moiety" in "esterified carboxy group" may include e.g. C_1—C_7 alkyl ester (e.g. methyl ester, ethyl ester, propyl ester, isopropyl ester, butyl ester, isobutyl ester, t-butyl ester, pentyl ester, tert-

pentyl ester, hexyl ester), C_2—C_7 alkenyl ester (e.g. vinyl ester, allyl ester), C_2—C_7 alkynyl ester (e.g. ethynyl ester, propynyl ester), C_1—C_7 alkoxy(C_1—C_7)alkyl ester (e.g. methoxymethyl ester, ethoxymethyl ester, isopropoxymethyl ester, 1-methoxyethyl ester, 1-ethoxyethyl ester), C_1—C_7 alkylthio(C_1—C_7)alkyl ester (e.g. methylthiomethyl ester, ethylthiomethyl ester, ethylthioethyl ester isopropylthiomethyl ester), amino- and carboxy-substituted-C_1—C_7 alkyl ester (e.g. 2-amino-2-carboxyethyl ester, 3-amino-3-carboxypropyl ester), protected amino- and protected carboxy-substituted-C_1—C_7 alkyl ester such as C_1—C_7 alkoxycarbonylamino- and mono- (or di to tri)phenyl(C_1—C_7)alkoxycarbonyl-substituted-C_1—C_7 alkyl ester (e.g. 2-tert-butoxycarbonylamino-2-benzhydryloxycarbonylethyl ester, 3-tert-butoxycarbonylamino-3-benzhydryloxycarbonylpropyl ester), mono (or di or tri)halo(C_1—C_7)alkyl ester (e.g. 2-iodoethyl ester, 2,2,2-trichloroethyl ester), C_1—C_7 alkanoyloxy(C_1—C_7)alkyl ester (e.g. acetoxymethyl ester, propionyloxymethyl ester, butyryloxymethyl ester, isobutylryloxymethyl ester, valeryloxymethyl ester, pivaloyloxymethyl ester, hexanoyloxymethyl ester, 2-acetoxyethyl ester, 2-propionyloxyethyl ester, 1-acetoxypropyl ester), C_1—C_7 alkanesulfonyl(C_1—C_7)alkyl ester (e.g. mesylmethyl ester, 2-mesylethyl ester), ar(C_1—C_7)alkyl ester which may have one or more substituent(s) such as mono (or di or tri)phenyl(C_1—C_7)alkyl ester which may have one or more suitable substituent(s) (e.g. benzyl ester, 4-methoxybenzyl ester, 4-nitrobenzyl ester, phenethyl ester, benzhydryl ester, trityl ester, bis(methoxyphenyl)methyl ester, 3,4-dimethoxybenzyl ester, 4-hydroxy-3,5-di-t-butylbenzyl ester), aryl ester which may have one or more suitable substituents (e.g. phenyl ester, tolyl ester, t-butylphenyl ester, xylyl ester, mesityl ester, cumenyl ester, salicyl ester) and heterocyclic ester (e.g. phthalidyl ester).

Suitable "protected phosphono group" may include e.g. O,O-di(C_1—C_7)alkylphosphono such as O,O-dimethylphosphono, O,O-diethylphosphono and O,O-dipropylphosphono.

Suitable "thiazolyl" and "thiadiazolyl" in the "aminothiazolyl which may have halogen" and "aminothiadiazolyl" for R^1 and R^1_b and "protected aminothiazolyl which may have halogen" and "protected aminothiadiazolyl" for R^1 and R^1_a may include thiazolyl and thiadiazolyl (e.g. 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl).

Suitable "C_1—C_7 alkoxycarbonyl(C_1—C_7)alkyl" group may include e.g. ethoxycarbonylmethyl, propoxycarbonylmethyl and 1- or 2-ethoxycarbonylethyl.

Suitable "C_1—C_7 alkoxycarbonyl" group may include e.g. ethoxycarbonyl and propoxycarbonyl.

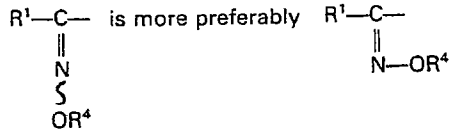
Suitable "halogen" may include e.g. chloro, bromo and iodo.

Suitable "aryl" group may include e.g. phenyl, tolyl, xylyl and naphthyl.

Suitable "protected oxo" group may include e.g. bis-(substituted-oxy) such as di(C_1—C_7)alkoxy (e.g. dimethoxy, diethoxy, dipropoxy) and C_1—C_7 alkylenedioxy (e.g. ethylenedioxy, trimethylenedioxy, propylenedioxy, tetramethylenedioxy, hexamethylenedioxy).

Particularly, the preferred embodiments of the terms "R^1", "$R^{2'}$" and "R^4" of the object compounds (I) are as follows.

The formula:



in which R^1 is aminothiazolyl which may have halogen (more preferably 2-aminothiazol-4-yl, 2-aminothiazol-5-yl, 2-amino-5-halothiazol-4-yl, or 4-aminothiazol-2-yl), aminothiadiazolyl (more preferably 5-amino-1,2,4-thiadiazol-3-yl), acylaminothiazolyl which may have halogen [more preferably 2-C_1—C_7 alkanamidothiazol-4-yl (e.g. 2-formamidothiazol-4-yl), 4-C_1—C_7 alkoxycarbonylaminothiazol-2-yl (e.g. 4-tert-butoxycarbonylaminothiazol-2-yl)], di(C_1—C_7)alkylaminomethyleneaminothiadiazolyl [more preferably 5-di-(C_1—C_7)alkylaminomethyleneamino-1,2,4-thiadiazol-3-yl (e.g. 5-dimethylaminomethyleneamino-1,2,4-thiadiazol-3-yl)], and R^4 is cyclo(C_2—C_7)alkenyl (e.g. cyclopentenyl, cyclohexenyl), C_2—C_7 alkynyl (e.g. propargyl), C_2—C_7 alkenyl (e.g. allyl), carboxy(C_2—C_7)alkenyl (e.g. 3-carboxyallyl), esterified carboxy(C_2—C_7)alkenyl [more preferably C_1—C_7 alkoxycarbonyl(C_2—C_7)alkenyl (e.g. 3-tert-butoxycarbonylallyl)], C_1—C_7 alkyl (e.g. methyl, ethyl, propyl, isopropyl, butyl, pentyl, hexyl), carboxy(C_1—C_7)alkyl (e.g. carboxymethyl, 1-carboxyethyl, 2-carboxyethyl, 3-carboxypropyl, 1-carboxy-1-methylethyl), esterified carboxy(C_1—C_7)alkyl [more preferably C_1—C_7 alkoxycarbonyl(C_1—C_7)alkyl (e.g. methoxycarbonylmethyl, ethoxycarbonylmethyl, tert-butoxycarbonylmethyl, 1-tert-butoxycarbonylethyl, 3-tert-butoxycarbonylpropyl, 1-tert-butoxycarbonyl-1-methylethyl), C_1—C_7 alkanoyloxy(C_1—C_7)alkoxycarbonyl(C_1—C_7)alkyl (e.g. acetoxymethoxycarbonylmethyl, pivaloyloxymethoxycarbonylmethyl, hexanoyloxymethoxycarbonylmethyl), amino- and carboxy-substituted-C_1—C_7 alkoxycarbonyl(C_1—C_7)alkyl (e.g. 2-amino-2-carboxyethoxycarbonylmethyl), C_1—C_7 alkoxycarbonylamino- and mono- or di- or triphenyl(C_1—C_7)alkoxycarbonyl-substituted-C_1—C_7 alkoxycarbonyl(C_1—C_7)alkyl (e.g. 2-tert-butoxycarbonylamino-2-benzhydryloxycarbonylethoxycarbonylmethyl)], amino- and carboxy-substituted-C_1—C_7 alkyl (e.g. 3-amino-3-carboxypropyl), acylamino- and esterified carboxy-substituted-C_1—C_7 alkyl [more preferably C_1—C_7 alkoxycarbonylamino- and mono- or di- or triphenyl(C_1—C_7)alkoxycarbonyl-substituted-C_1—C_7 alkyl (e.g. 3-tert-butoxycarbonylamino-3-benzhydryloxycarbonylpropyl)],

cyano(C_1—C_7)alkyl (e.g. cyanomethyl, cyanoethyl, etc.), phosphono(C_1—C_7)alkyl (more preferably phosphonomethyl, phosphonoethyl), esterified phosphono(C_1—C_7)alkyl [more preferably O,O-dialkylphosphono(C_1—C_7)alkyl (e.g. O,O-dimethylphosphonomethyl, O,O-diethylphosphonomethyl)] or pyridyl(C_1—C_7)alkyl (e.g. 2- or 3-pyridylmethyl).

The term "R^2" is carboxy or esterified carboxy group [more preferably mono- or di- or triphenyl(C_1—C_7)alkoxycarbonyl (e.g. benzhydryloxycarbonyl), C_1—C_7 alkanoyloxy(C_1—C_7)alkoxycarbonyl (e.g. acetoxymethoxycarbonyl, propionyloxymethoxycarbonyl, isobutyryloxymethoxycarbonyl, pivaloyloxymethoxycarbonyl, hexanoyloxymethoxycarbonyl, 1-acetoxypropoxycarbonyl), amino- and carboxy-substituted C_1—C_7 alkoxycarbonyl (e.g. 2-amino-2-carboxyethoxycarbonyl), C_1—C_7 alkoxycarbonylamino- and mono or di- or triphenyl(C_1—C_7)alkoxycarbonyl-substituted-(C_1—C_7)alkoxycarbonyl (e.g. 2-tert-butoxycarbonylamino-2-benzhydryloxycarbonylethoxycarbonyl), phthalidyl (e.g. phthalid-3-yl)].

Suitable intramolecular or intermolecular quaternary salt of the object compounds (I) may include 7-[2-(2-aminothiazol-4-yl)-2-{(1-methyl-3-pyridinio)methoxyimino}acetamido]-3-vinyl-3-cephem-4-carboxylate,

7-[2-(2-aminothiazol-4-yl)-2-{(1-methyl-2-pyridinio)methoxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylate,

1-methyl-3-[1-(2-aminothiazol-4-yl)-1-{N-(4-benzhydryloxycarbonyl-3-vinyl-3-cephem-7-yl)carbamoylmethyleneaminooxymethyl]pyridinium methylsulfate,

1-methyl-2-[1-(2-aminothiazol-4-yl)-1-{N-(4-benzhydryloxycarbonyl-3-vinyl-3-cephem-7-yl)carbamoyl}-methyleneaminooxymethyl]pyridinium methylsulfate.

The processes 1 to 13 for the preparation of the object compounds (I) of the present invention are explained in detail in the following.

(1) Process 1:

The compounds (I) or a salt thereof can be prepared by reacting the compound (II) or its reactive derivative at the amino group or a salt thereof with the compound (III) or its reactive derivative at the carboxy group or a salt thereof.

Suitable salts of the starting compounds (II) and (III) may include the same ones as illustrated for the compounds (I).

Suitable reactive derivative at the amino group of the compound (II) may include e.g. a conventional one, for example, a silyl derivative formed by the reaction of the compound (II) with a silyl compound such as bis-(trimethylsilyl)acetamide, trimethylsilylacetamide, etc.; isocyanate; isothiocyanate; Schiff's base or its tautomeric enamine type isomer formed by the reaction of the amino group with a carbonyl compound such as an aldehyde compound (e.g. acetaldehyde, isopentaldehyde, benzaldehyde, salicylaldehyde, phenylacetaldehyde, p-nitrobenzaldehyde, m-chlorobenzaldehyde, p-chlorobenzaldehyde, hydroxynaphthoaldehyde, furfural, thiophenecarboaldehyde) or a ketone compound (e.g. acetone, methyl ethyl ketone, methyl isobutyl ketone and acetylacetone, ethyl acetoacetate).

Suitable reactive derivative of the compound (III) may include, for example, an acid halide, an acid anhydride, an activated amide and an activated ester, and preferably an acid chloride and acid bromide; a mixed acid anhydride with an acid such as substituted phosphoric acid (e.g. dialkylphosphoric acid, phenylphosphoric acid, diphenylphosphoric acid, dibenzylphosphoric acid, halogenated phosphoric acid), dialkylphosphorous acid, sulfurous acid, thiosulfuric acid, sulfuric acid, alkyl carbonate (e.g. methyl carbonate, ethyl carbonate, propyl carbonate), aliphatic carboxylic acid (e.g. pivalic acid, pentanoic acid, isopentanoic acid, 2-ethylbutyric acid, trichloroacetic acid), aromatic carboxylic acid (e.g. benzoic acid); a symmetrical acid anhydride; an activated acid amide with a heterocyclic compound containing imino function such as imidazole, 4-substituted imidazole, dimethylpyrazole, triazole or tetrazole; and an activated ester (e.g. p-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachlorophenyl, ester, mesylphenyl ester, phenylazophenyl ester, phenyl thioester, p-nitrophenyl thioseter, p-cresyl thioester, carboxymethyl thioester, pyridyl ester, piperidinyl ester, 8-quinolyl thioester, or an ester with a N-hydroxy compound such as N,N-dimethylhydroxylamine, 1-hydroxy-2-(1H)-pyridone, N-hydroxysuccinimide, N-hydroxyphthalimide, 1-hydroxybenzotriazole, 1-hydroxy-6-chlorobenzotriazole).

The suitable reactive derivative can optionally be selected from the above according to the kinds of the compounds (II) and (III) to be used practically.

This reaction can be carried out in the presence of e.g. an organic or inorganic base such as alkali metal (e.g. lithium, sodium, potassium), alkaline earth metal (e.g. calcium), alkali metal hydride (e.g. sodium hydride), alkaline earth metal hydride (e.g. calcium hydride), alkali metal hydroxide (e.g. sodium hydroxide, potassium hydroxide), alkali metal carbonate (e.g. sodium carbonate, potassium carbonate), alkali metal bicarbonate (e.g. sodium bicarbonate, potassium bicarbonate), alkali metal alkoxide (e.g. sodium methoxide, sodium ethoxide, potassium tert-butoxide), alkali metal alkanoic acid (e.g. sodium acetate), trialkylamine (e.g. triethylamine), pyridine compound (e.g. pyridine, lutidine, picoline) and quinoline.

In case that the compound (III) is used in a form of the free acid or a salt in this reaction, the reaction is preferably carried out in the presence of a condensing agent such as a carbodiimide compound [e.g. N,N'-dicyclohexylcarbodiimide, N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide, N,N'-diethylcarbodiimide, N,N'-diisopropylcarbodiimide, N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide], a

ketenimine compound (e.g. N,N'-carbonylbis(2-methylimidazole), pentamethyleneketene-N-cyclohexylimine, diphenylketene-N-cyclohexylimine); an olefinic or acetylenic ether compounds (e.g. ethoxyacetylene, β-chlorovinylethyl ether), a sulfonic acid ester of N-hydroxybenzotriazole derivative [e.g. 1-(4-chlorobenzenefulfonyloxy)-6-chloro-1H-benzotriazole], a combination of trialkylphosphite or triphenylphosphine and carbon tetrachloride, disulfide or diazenedicarboxylate (e.g. diethyl diazenedicarboxylate), a phosphorus compound (e.g. ethyl polyphosphate, isopropyl polyphosphate, phosphoryl chloride, phosphorus trichloride), thionyl chloride, oxalyl chloride, N-ethylbenzisoxazolium salt, N-ethyl-5-phenylisoxazolium-3-sulfonate, a reagent (referred to as so-called "Vilsmeier reagent") formed by the reaction of an amide compound such as N,N-di(lower)alkylformamide (e.g. dimethylformamide) or N-methylformamide with a halogen compound such as thionyl chloride, phosphoryl chloride or phosgene.

The reaction is usually carried out in a conventional solvent which does not adversely influence the reaction such as water, acetone, dioxane, acetonitrile, chloroform, benzene, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine and hexamethylphosphoramide, or a mixture thereof.

Among these solvents, hydrophilic solvents may be used in a mixture with water.

The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

The present invention includes, within the scope thereof, in case that the reaction is carried out in the presence of Vilsmeier reagent mentioned above, the amino group for R^1 in the starting compound (III) is occasionally transformed into a (N,N-di(lower)alkylaminomethylene)amino group during the reaction.

(2) Process 2:

The compound (I-b) or a salt thereof can be prepared by subjecting the compound (I-a) or a salt thereof to removal reaction of the amino-protective group in R^1_a.

Suitable method for this removal reaction may include conventional one such as hydrolysis, reduction, combined methods comprising iminohalogenation and then iminoetherification, followed by hydrolysis, if necessary, and the like.

(i) For hydrolysis:

Hydrolysis is preferably carried out in the presence of an acid.

Suitable acid may be e.g. an inorganic acid (e.g. hydrochloric acid, hydrobromic acid, sulfuric acid), an organic acid (e.g. formic acid, acetic acid, trifluoroacetic acid, propionic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid) and an acidic ion-exchange resin. In case that the organic acid such as trifluoroacetic acid and p-toluenesulfonic acid is used in this reaction, the reaction is preferably carried out in the presence of cation trapping agents (e.g. anisole).

The acid suitable for this hydrolysis can be selected according to the kinds of the protective group to be removed, for example, this hydrolysis can preferably be applied to the amino-protective group for R^1_a such as substituted or unsubstituted C_1—C_7 alkoxycarbonyl, substituted or unsubstituted C_1—C_7 alkanoyl.

The hydrolysis is usually carried out in a conventional solvent which does not adversely influence the reaction such as water, methanol, ethanol, propanol, tert-butyl alcohol, tetrahydrofuran, N,N-dimethylformamide, dioxane or a mixture thereof, and further the above-mentioned acids can also be used as a solvent when they are in liquid.

The reaction temperature of this hydrolysis is not critical, and the reaction is usually carried out under cooling to at somewhat elevated temperature.

(ii) For Reduction:

Reduction is carried out in a conventional manner, including chemical reduction and catalytic reduction.

Suitable reducing agents to be used in chemical reduction are a combination of a metal (e.g. tin, zinc, iron) or metallic compound (e.g. chromium chloride, chromium acetate) and an organic or inorganic acid (e.g. formic acid, acetic acid, propionic acid, trifluoroacetic acid, p-toluenesulfonic acid, hydrochloric acid, hydrobromic acid.

Suitable catalysts to be used in catalytic reduction are conventional ones such as platinum catalysts (e.g platinum plate, spongy platinum, platinum black, colloidal platinum, platinum oxide, platinum wire), palladium catalysts (e.g spongy palladium, palladium black, palladium oxide, palladium on carbon, colloidal palladium, palladium on barium sulfate, palladium on barium carbonate), nickel catalysts (e.g. reduced nickel, nickel oxide, Raney nickel), cobalt catalysts (e.g. reduced cobalt, Raney cobalt), iron catalysts (e.g. reduced iron, Raney iron) and copper catalysts (e.g. reduced copper, Raney copper, Ullman copper).

The reduction manner can be selected according to the kinds of the protective group to be removed, for example, the chemical reduction can preferably be applied to the amino-protective group for R^1_a such as halo(C_1—C_7)alkoxycarbonyl, and catalytic reduction can preferably be applied to that such as substituted or unsubstituted ar(C_1—C_7)alkoxycarbonyl.

The reduction is usually carried out in a conventional solvent which does not adversely influence the reaction such as water, methanol, ethanol, propanol, N,N-dimethylformamide, or a mixture thereof. Additionally, in case that the above-mentioned acids to be used in chemical reduction are in liquid, they can

also be used as a solvent. Further, a suitable solvent to be used in catalytic reduction may be the above-mentioned solvent, and other conventional solvent such as diethyl ether, dioxane, tetrahydrofuran, or a mixture thereof.

The reaction temperature of this reduction is not critical and the reaction is usually carried out under cooling to warming.

(iii) For combined methods comprising iminohalogenation (the first step) and then iminoetherification (the 2nd step), followed by hydrolysis (the last step), if necessary:

The first and second steps of this method are preferably carried out in an anhydrous solvent. Suitable solvent for the first step (i.e. iminohalogenation) is an aprotic solvent such as methylene chloride, chloroform, diethyl ether, tetrahydrofuran, dioxane, etc., and for the second step (i.e. iminoetherification) is usually the same as those in the above first step. These two steps are usually conducted under cooling to at ambient temperature. These two steps and the last step (i.e. hydrolysis step) are most preferably conducted in one-batch system.

Suitable iminohalogenating agents include a halogenating agent such as phosphorus halo compound (e.g. phosphorus trichloride, phosphorus pentachloride, phosphorus tribromide, phosphorus pentabromide, phosphorus oxychloride) and thionyl chloride, phosgene.

Suitable iminoetherifying agent may be an alcohol such as an alkanol (e.g. methanol, ethanol, propanol, isopropanol, butanol) or the corresponding alkanol having alkoxy (e.g. 2-methoxyethanol, 2-ethoxyethanol), and alkoxide of metal such as alkali metal and alkaline earth metal (e.g. sodium methoxide, potassium ethoxide, magnesium ethoxide, lithium methoxide.

Thus obtained reaction product is, if necessary, hydrolyzed in a conventional manner.

The hydrolysis is preferably carried out at ambient temperature to under cooling, and proceeds simply pouring the reaction mixture into water or a hydrophilic solvent such as alcohol (e.g. methanol, ethanol) moistened or admixed with water, and if necessary, with addition of an acid or base.

Suitable acid may include the same ones as those given in the explanation of Hydrolysis mentioned in the above item (i), and suitable base may include the same ones as those given in the explanation of Process 1.

The methods thus explained may be selected depending upon the kind of the protective groups to be removed.

The present invention includes, within the scope of the invention cases that the protected amino group and/or the protected carboxy group in R^2 and R^4 are transformed into free amino group and/or free carboxy group, respectively during the reaction.

(3) Process 3:

The compound (I-d) or a salt thereof can be prepared by subjecting the compound (I-c) or a salt thereof to removal reaction of the carboxy-protective group for R^2_a.

This reaction is carried out by a conventional method such as hydrolysis, reduction, and the like.

The method of hydrolysis and reduction, and the reaction conditions (e.g. reaction temperature and solvent) are substantially the same as those illustrated for the removal reaction of the amino-protective group of the compound (I-a) in Process 2, and therefore are to be referred to said explanation.

The present invention includes, within the scope of the invention, cases that the protected amino group in R^1 and R^4 and/or the protected carboxy group in R^4 are transformed into free amino group(s) and/or a free carboxy group, respectively during the reaction.

(4) Process 4:

The compound (I-c) or a salt thereof can be prepared by introducing a carboxy-protective group into the compound (I-d) or a salt thereof.

The introducing agent of a carboxy-protective group to be used in this reaction may include e.g. conventional esterifying agent such as an alcohol or its reactive equivalent (e.g. halide, sulfonate, sulfate, diazo compound).

The reaction can also be carried out in the presence of a base, and suitable examples thereof are the same as those given in the explanation of Process 1, and can preferably be carried out in the presence of metal iodide (e.g. sodium iodide).

This reaction is usually carried out in a conventional solvent which does not adversely influence the reaction such as N,N-dimethylformamide, tetrahydrofuran, dioxane, methanol, ethanol, or a mixture thereof.

The reaction temperature is not critical, and the reaction is usually carried out under cooling to at somewhat elevated temperature.

In case that the alcohol is used as the introducing agent of a carboxy-protective group, the reaction can be carried out in the presence of a condensing agent as illustrated in Process 1.

The present invention includes, within the scope thereof, the case that the carboxy-protective group is occasionally introduced into the carboxy group in R^4 of the compound (I-d) during the reaction.

(5) Process 5:

The compound (I-e) or a salt thereof can be prepared by reacting the compound (IV) or a salt thereof with the compound (V).

Suitable salts of the starting compound (IV) may include the same salts with a base for the compounds (I).

This reaction is usually carried out in a conventional solvent which does not adversely influence the reaction such as ethyl acetate, methylene chloride, chloroform, carbon tetrachloride, tetrahydrofuran, dioxane, water, or a mixture thereof.

The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

(6) Process 6:

The compound (I-g) or a salt thereof can be prepared by subjecting the compound (I-f) or a salt thereof to removal reaction of the carboxy-protective group or the phosphono-protective group in R^4_a.

This reaction is carried out by a conventional method such as hydrolysis, reduction, and the like.

The method of hydrolysis and reduction, and the reaction conditions (e.g. reaction temperature, solvent), are substantially the same as those illustrated for the removal reaction of the amino-protective group of the compound (I-a) in Process 2, and therefore are to be referred to said explanation.

Further, for removal reaction of the phosphono protective group, the reaction can also be carried out by reacting the compound (I-f) with trialkylsilyl halide such as trimethylsilyl chloride, trimethylsilyl bromide and trimethylsilyl iodide.

The present invention includes, within the scope thereof, cases that the protected amino group in R^1 and R^2, and/or the protected carboxy group in R^2 are transformed into free amino group and/or free carboxy group, respectively during the reaction.

(7) Process 7:

The compound (I) or a salt thereof can be prepared by reacting the compound (VI) or a salt thereof with formaldehyde.

Suitable salts of the compound (VI) may include the same ones as exemplified for the compounds (I).

This reaction is usually carried out in a conventional solvent which does not adversely influence the reaction such as tetrahydrofuran, dioxane, or a mixture thereof.

The reaction temperature is not critical and the reaction is usually carried out under cooling to somewhat elevated temperature.

(8) Process 8:

The compound (I-i) or a salt thereof can be prepared by subjecting the compound (I-h) or a salt thereof to removal reaction of the amino- and carboxy-protective groups in R^2_b.

This reaction is carried out by a conventional method such as hydrolysis and reduction.

The method of hydrolysis and reduction, and the reaction conditions (e.g. reaction temperature, solvent) are substantially the same as those illustrated for removal reaction of the amino-protective group of the compound (I-a) in Process 2, and therefore are to be referred to said explanation.

In this reaction, the amino- and carboxy-protective groups can be removed separately or at a time.

The present invention includes, within the scope thereof, cases that the protected amino group in R^1 and R^4 and/or the protected carboxy group in R^4 are transformed into free amino group and/or free carboxy group, respectively during the reaction.

(9) Process 9:

The compound (I-k) or a salt thereof can be prepared by subjecting the compound (I-j) or a salt thereof to removal reaction of the amino- and carboxy-protective groups in R^4_c.

This reaction is carried out by a conventional method such as hydrolysis and reduction.

The method of hydrolysis and reduction, and the reaction conditions (e.g. reaction temperature and solvent) are substantially the same as those illustrated for removal reaction of the amino-protective group of the compound (I-a) in Process 2, and therefore are to be referred to said explanation.

In this reaction, the amino- and carboxy-protective groups can be removed separately or at a time.

The present invention includes, within the scope thereof, cases that the protected amino group in R^1 and R^2 and/or the protected carboxy group in R^2 are transformed into free amino group and/or free carboxy group, respectively during the reaction.

(10) Process 10:

The compound (I-f) or a salt thereof can be prepared by introducing a carboxy-protective group or a phosphono-protective group into the compound (I-g) or a salt thereof.

This reaction is carried out by substantially the same method as that illustrated for introducing the carboxy-protective group into the compound (I-d) in Process 4, and therefore, the reaction conditions (e.g. reaction temperature and solvent) are to be referred to said explanation.

The present invention includes, within the scope thereof, case that the carboxy group for R^2 is transformed into the protected carboxy group during the reaction.

(11) Process 11:

The compound (I-m) or a salt thereof can be prepared by reacting the compound (I-l) or a salt thereof with the compound (VII).

This reaction is usually carried out in a conventional solvent which does not adversely influence the reaction such as tetrahydrofuran, dioxane, water or a mixture thereof.

The reaction temperature is not critical, and the reaction is usually carried out at ambient temperature to under heating.

(12) Process 12:

The compound (I-o) or a salt thereof can be prepared by reacting the compound (I-n) or a salt thereof with a base.

Suitable base used in this Process may include the same ones as those exemplified in Process 1.

This reaction is usually carried out in a conventional solvent which does not adversely influence the reaction such as water, methanol, ethanol or a mixture thereof.

The reaction temperature is not critical, and the reaction is usually carried out under cooling to warming.

(13) Process 13:

The compound (I) or a salt thereof can be prepared by reacting the compound (I-r) or a salt thereof with the compound (VIII) or a salt thereof.

The starting compound (I-r) can be prepared according to methods described in preparations.

Suitable salts of the compound (VIII) may include the same acid addition salts as exemplified for the compounds (I).

In this reaction, when the compound (VIII) is used in a salt form, this reaction can also be carried out in the presence of a base as exemplified in Process 1.

This reaction is usually carried out in a conventional solvent which does not adversely influence the reaction such as water, methanol, ethanol, propanol, dioxane, tetrahydrofuran or a mixture thereof.

The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

The object compounds (I) obtained according to the Processes 1 to 13 as explained above can be isolated and purified in a conventional manner, for example, extraction, precipitation, fractional crystallization, recrystallization and chromatography.

Process ① to ⑩ for the preparation of the starting compounds are explained in detail in the following.

Process ①-(1):

The compound (①-b) or a salt thereof can be prepared by reacting the compound (①-a) or a salt thereof with the halogenating agent.

Suitable salts of the compounds (①-a) and (①-b) may include the same salt with a base as exemplified for the compounds (I).

Suitable halogenating agents used in this reaction may include one which can be applied to conversion of a hydroxy group to halo group such as phosphorus halide (e.g. phosphorus trichloride, phosphorus pentachloride, phosphorus oxychloride, phosphorus tribromide, phosphorus pentabromide, thionyl halide (e.g. thionyl chloride and phosgene.

The reaction is preferably carried out in the presence of a base such as an organic base given in the explanation of Process 1.

This reaction is usually carried out in a conventional solvent which does not adversely influence the reaction such as methylene chloride, chloroform, ethylene chloride, tetrathydrofuran, dioxane, N,N-dimethylformamide or a mixture thereof.

The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

Process ①-②:

The compound (①-c) or a salt thereof can be prepared by reacting the compound (①-b) or a salt thereof with a trisubstituted phosphine (IX) of the formula: $P(R^7)_3$, wherein R^7 is as defined above.

Suitable salts of the compound (①-c) may include the same salt with a base as exemplified for the compounds (I).

This reaction is preferably carried out in the presence of metal halide such as alkali metal halide (e.g. sodium iodide, potassium iodide, sodium bromide) and in such a case, the halogen for X^2 of the compound (①-b) can be replaced with the halo moiety of such metal halide in the object compound (①-c) during the reaction.

This reaction is usually carried out in a conventional solvent which does not adversely influence the reaction such as N,N-dimethylformamide, dimethylsulfoxide, methylene chloride, tetrahydrofuran, ethyl acetate or a mixture thereof.

The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

Process ①-(3):

The compound (①-d) or a salt thereof can be prepared by reacting the compound (①-c) or a salt thereof with a base.

Suitable salts of the compound (①-d) may include the same salt with a base as exemplified for the compounds (I).

Suitable base used in this process are the same as those given in the explanation of Process 1.

This reaction is usually carried out in a conventional solvent which does not adversely influence the reaction such as acetone, tetrahydrofuran, water or a mixture thereof.

The reaction temperature is not critical and the reaction is usually carried out under cooling to at somewhat elevated temperature.

Process ①-(4):

The compound (①-f) or a salt thereof can be prepared by reacting the compound (①-e) or its reactive derivative at the amino group or a salt thereof with the compound (III) or its reactive derivative at the carboxy group or a salt thereof.

Suitable salts of the compound (①-e) may include the same ones as exemplified for the compounds (I), and suitable salts of the compounds (①-f) may include the same salt with a base as exemplified for the compounds (I).

Suitable reactive derivative of the compounds (①-e) may include the same ones as exemplified for the compounds (II) in Process 1, respectively.

The reaction is substantially the same method as Process 1, and accordingly, the method, reaction conditions (e.g. reaction temperature, solvent and base) are to be referred to said explanation.

Process ②-(1):

The compound (②-b) or a salt thereof can be prepared by reacting the compound (②-a) or a salt thereof with formaldehyde.

Suitable salts of the compounds (②-a) and (②-b) may include the same ones as exemplified for the compounds (I).

This reaction can be carried out by substantially the same method as that illustrated for Process 7, and therefore reaction conditions (e.g. reaction temperature and solvent) are to be referred to said explanation.

Process ②-(2):

The compound (②-d) or a salt thereof can be prepared by subjecting the compound (②-c) or a salt thereof to removal reaction of the carboxy-protective group.

Suitable salts of the compound (②-c) may include the same acid addition salts as exemplified for the compounds (I), and suitable salts of the compound (②-d) may include the same ones as exemplified for the same compounds.

This reaction is carried out by a conventional method such as hydrolysis.

The hydrolysis is carried out by substantially the same method as that illustrated for Process 2, and therefore the method of hydrolysis and the reaction conditions (e.g. reaction temperature and solvent) are referred to said explanation.

Process ②-(3):

The compound (②-f) or a salt thereof can be prepared by reacting the compound (②-e) or its reactive derivative at the amino group or a salt thereof with the compound (X) or its reactive derivative at the carboxy group or a salt thereof.

Suitable salts of the compound (②-e) may include the same ones as exemplified for the compounds (I), and suitable salts of the compounds (②-f) and (X) may include the same salts with a base as exemplified for the compounds (I).

Suitable reactive derivative at the amino group of the compound (②-e) and that at the carboxy group of the compound (X) may include the same ones as exemplified for the compounds (II) and (III) in Process 1.

The reaction is substantially the same method as Process 1, and accordingly, the method, reaction conditions (e.g. reaction temperature, solvent and base) are to be referred to said explanation.

Process ②-(4):

The compound (IV) or a salt thereof can be prepared by subjecting the compound (②-g) or a salt thereof to removal reaction of the oxo-protective group.

Suitable salts of the compound (②-g) may include the same salt with a base as exemplified for the compounds (I).

This reaction is carried out by a conventional method such as hydrolysis.

The method of hydrolysis, and the reaction conditions (e.g. reaction temperature and solvent) are substantially the same as those illustrated for Process 2, and therefore are to be referred to said explanation.

Process ③-(1):

The compound (③-b) or a salt thereof can be prepared by reacting the compound (③-a) or a reactive derivative at the carboxy group or a salt thereof with C_1—C_7 alkanol substituted by protected amino and protected carboxy groups (XI).

Suitable salts of the compounds (③-a) and (③-b) may include the same ones as exemplified for the compounds (I).

Suitable reactive derivative at the carboxy group of the compound (③-a) may include the same ones as the compound (III) in Process 1.

This reaction is carried out by substantially the same method as that illustrated for Process 4, and therefore, the reaction conditions (e.g. reaction temperature and solvent) are to be referred to said explanation.

Process (③-(2):

The compound (③-c) or a salt thereof can be prepared by subjecting the compound (③-b) or a salt thereof to removal reaction of the amino-protective group in R_0'.

Suitable salt of the compound (③-c) may include the same ones as exemplified for the compounds (I).

This reaction is carried out by substantially the same method as that illustrated for Process 2, and therefore, the reaction conditions (e.g. reaction temperature and solvent) are to be referred to said explanation.

Process ④-(1):

The compound (④-f) or a salt thereof can be prepared by reacting the compound (④-e) or a salt thereof can be prepared by reacting the compound (④-e) or a salt thereof with the compound (XIII) or a salt thereof.

Suitable salts of the compounds (④-e), (④-f) and (XIII) may include the same salt with a base as exemplified for the compounds (I).

This reaction is usually carried out in a conventional solvent which does not adversely influence the reaction such as diethyl ether, diisopropyl ether, or a mixture thereof.

The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

Process ④-(2):

The compound (④-g) or a salt thereof can be prepared by subjecting the compound (④-f) or a salt thereof to azidation (the first step) and then, subjecting the resultant compound to a thermal degradation reaction (the second step), followed by treating the resultant compound with the alcohol (the last step).

Suitable salts of the compound (④-g) may include the same salt with a base as exemplified for the compounds (1).

(i) As to the first step:

Suitable azidating agent may include hydrazoic acid or its reactive derivative such as sodium azide, potassium azide, calcium azide and diphenylphosphorous azide.

This reaction is usually carried out in a conventional solvent which does not adversely influence the reaction such as alcohol mentioned below, tetrahydrofuran, dichloromethane, diethyl ether, or a mixture thereof.

The reaction temperature is not critical and the reaction is usually carried out under cooling to be at ambient temperature.

(ii) As to the second step:

This reaction can be carried out by heating the resulting compound obtained in the first step. This reaction is usually carried out in a conventional solvent as mentioned in the first step.

(iii) As to the last step:

This reaction can be carried out by adding alcohol.

Suitable alcohol may include e.g. C_1—C_7 alkanol (e.g. methanol, ethanol, propanol, butanol, tert-butanol, etc.) and ar(C_1—C_7)alkanol (e.g. benzyl alcohol, benzhydryl alcohol).

The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

A chain of these steps mentioned above can also be carried out by one pot.

Process ④-(3):

The compound (④-h) or a salt thereof can be prepared by reacting the compound (④-g) or a salt thereof with an oxidizing agent.

Suitable salts of the compound (④-h) may include the same salt with a base as exemplified for the compounds (I).

Suitable oxidizing agent may include one which is applied for the transformation of so-called activated methylene group into carbonyl group such as selenium dioxide.

The present reaction is usually carried out in a conventional solvent which does not adversely influence the reaction such as tetrahydrofuran, dioxane or a mixture thereof.

The reaction temperature is not critical and the reaction is preferably carried out under warming to heating.

Process ④-(4):

The compound (④-i) or a salt thereof can be prepared by reacting the compound (④-h) or a salt thereof with the compound(VIII) or a salt thereof.

Suitable salts of the compound (④-1) may include the same salt with a base as exemplified for the compounds (I), and suitable salts of the compound (VIII) may include the same acid addition salt as exemplified for the same compounds.

This reaction is carried out by substantially the same method as that of Process 13, and therefore the reaction conditions (e.g. reaction temperature, solvent and base) are to be referred to said explanation.

Process ④-(5):

The compound (④-k) or a salt thereof can be prepared by subjecting the compound (④-j) or a salt thereof to removal reaction of the carboxy-protective group for R^1.

Suitable salts of the compound (④-k) may include the same ones as exemplified for the compounds (I), and suitable salts of the compound (④-j) may include the same acid addition salt as exemplified for the same compounds.

This reaction is carried out by conventional method such as hydrolysis and reduction.

The method of hydrolysis and reduction, and the reaction conditions (e.g. reaction temperature and solvent) are substantially the same as those illustrated for Process 2, and therefore are to be referred to said explanation.

Process ⑤:

The compound (⑤-b) or a salt thereof can be prepared by reacting the compound (⑤-a) or a salt thereof with the compound (XV) or a salt thereof.

Suitable salts of the compounds (⑤-a), (⑤-b) and (XV) may include the same ones as exemplified for the compounds (I).

This reaction is carried out by substantially the same method as that of Process 13, and therefore the reaction conditions (e.g. reaction temperature, solvent and base) are to be referred to said explanation.

Process ⑥:

The compound (⑥-b) or a salt thereof can be prepared by reacting the compound (⑥-a) or a salt thereof with the compound (XVI) or a salt thereof.

Suitable salts of the compounds (⑥-a), (⑥-b) and (XVI) may include the same ones as exemplified for the compounds (I).

This reaction is carried out by substantially the same method as that of Process 13, and therefore the reaction conditions (e.g. reaction temperature, solvent and base) are to be referred to said explanation.

Process ⑦)(1):

The compound (⑦-b) can be prepared by reacting the compound (⑦-a) or a reactive derivative at the hydroxy group with N-hydroxyphthalimide or a salt thereof.

Suitable salts of N-hydroxypthalimide may include the alkali metal salt as exemplified for the compounds (I).

Suitable reactive derivatives at the hydroxy group may include halide such as chloride and bromide.

This reaction is preferably carried out in the presence of a base as exemplified in Process 1.

In case that the compound (⑦-a) is used in a free form, the reaction can usually be carried out in the presence of a condensing agent as exemplified in Process 1.

This reaction is usually carried out in a conventional solvent which does not adversely influence the reaction such as tetrahydrofuran, N,N-dimethylformamide acetonitrile or a mixture thereof.

The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

Process ⑦-(2):

The compound (⑦-c) or a salt thereof can be prepared by subjecting the compound (⑦-b) to removal reaction of the phthaloyl group.

Suitable salt of the compound (⑦-c) may include the same acid addition salt as exemplified for the compounds (I).

This reaction is carried out by a conventional method such as hydrolysis.

The method of hydrolysis, and the reaction conditions (e.g. reaction temperature and solvent) are substantially the same as those illustrated for Process 2, and therefore are to be referred to said explanation.

Process ⑧:

The compound (⑧-b) or a salt thereof can be prepared by subjecting the compound (⑧-a) to removal reaction of the acyl group.

Suitable salts of the compound (⑧-b) may include the same acid addition salts as exemplified for the compounds (I).

This reaction is usually carried out by combined methods comprising iminohalogenation and the iminoetherification, followed by hydrolysis, if necessary.

These combined methods and reaction conditions (e.g. reaction temperature and solvent) are substantially the same as those illustrated for Process 2, and therefore are to be referred to said explanation.

Process ⑨:

Step 1:—

The compound (⑨-b) or a salt thereof can be prepared by subjecting the compound (⑨-a) or a salt thereof to removal reaction of the acyl group.

Suitable salts of the compound (⑨-a) may include the same salt with a base as exemplified for the compounds (I), and suitable salts of the compound (⑨-b) may include the same ones as exemplified for the same compounds (I).

This reaction can be carried out by combined methods comprising iminohalogenation and then iminoetherification, followed by hydrolysis, if necessary.

The combined methods and the reaction conditions (e.g. reaction temperature and solvent) are substantially the same as those illustrated for Process 2, and therefore are to be referred to said explanation.

Step 2:—

The compound (⑨-c) or a salt thereof can be prepared by reacting the compound (⑨-b) or a salt thereof with the compound (XVII) of the formula: R^8—CHO, wherein R^8 is as defined above.

Suitable salts of the compound (⑨-c) may include the same salt with a base as exemplified for the compounds (I).

This reaction is preferably carried out in the presence of a dehydrating agent such as molecular sieve.

This reaction is usually carried out in a conventional solvent which does not adversely influence the reaction such as N,N-dimethylformamide.

The reaction temperature is not critical and the reaction is usually carried out at ambient temperature to under heating.

Process ⑩:

The compound (⑩-b) or a salt thereof can be prepared by reducing the compound (⑩-a) or a salt thereof.

Suitable salts of the compounds (⑩-a) and (⑩-b) may include the same ones as exemplified for the compounds (I).

This reaction is carried out by a conventional method such as catalytic reduction e.g. using a reducing agent.

The method of catalytic reduction and the reaction conditions (e.g. reaction temperature and solvent) are substantially the same as those illustrated for Process 2, and therefore are to be referred to said explanation.

Further, suitable reducing agent may include e.g. borane and diborane.

The starting compounds thus prepared can be isolated in a conventional manner as mentioned for the object compounds of the present invention.

It is to be noted that, in the aforementioned reactions in Processes 1 to 13 and ① to ⑩ or the post-treatment of the reaction mixture therein, in case that the starting compounds possess an optical and/or geometrical isomer(s), it may occasionally be transformed into the other optical and/or geometrical isomer(s), and such cases are also included within the scope of the present invention.

In case that the object compounds (I) have a free carboxy group or free amino group at the 4th or 7th position thereof, it may be transformed into its pharmaceutically acceptable salts by a conventional method.

The object compounds (I) and the pharmaceutically acceptable salts thereof of the present invention are novel and exhibit high antimicrobial activity, inhibiting the growth of a wide variety of pathogenic microorganisms including Gram-positive and Gram-negative microorganisms and are useful as antimicrobial agents, especially for oral administration as shown in the following data.

Now in order to show the utility of the object compounds (I), the test data on the antimicrobial activity of some representative compounds (I) of this invention are shown in the following.

(1) Test 1: in vitro Antimicrobial Activities.

Test Compounds

No. 1 7-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid (syn isomer) (hereinafter referred to as Compound A).

No. 2 7-[2-(2-Aminothiazol-4-yl)-2-ethoxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid (syn isomer) (hereinafter referred to as Compound B).

No. 3 7-[2-(2-Aminothiazol-4-yl)-2-hexyloxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid (syn isomer) (hereinafter referred to as Compound C).

No. 4 7-[2-(2-Aminothiazol-4-yl)-2-(L-2-amino-2-carboxyethoxycarbonylmethoxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid (syn isomer) (hereinafter referred to as Compound D).

No. 5 7-[2-(2-Aminothiazol-4-yl)-2-carboxymethoxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid (syn isomer) (hereinafter referred to as Compound E).

No. 6 7-[2-(2-Amino-5-chlorothiazol-4-yl)-2-carboxymethoxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid (syn isomer) (herinafter referred to as Compound F).

No. 7 7-[2-(2-Aminothiazol-4-yl)-2-(trans-3-carboxy-allyloxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid (syn isomer) (hereinafter referred to as Compound G).

No. 8 7-[2-(2-Aminothiazol-4-yl)-2-(3-carboxypropoxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid (syn isomer) (hereinafter referred to as Compound H).

Test Method

In vitro Antimicrobial activity was determined by the two-fold agar-plate dilution method as described below.

One loopful of an overnight culture of each test strain in Tripticase-soy broth (aproximately 10^8 viable cells per ml) was streaked on heart infusion agar (HI-agar) containing graded concentrations of antimicrobial agents, and the minimal inhibitory concentration (MIC) was expressed in term of µg/ml after incubation at 37°C for 20 hours.

Test Results 1

MIC (µg/ml)

Microorganisms / Test Compounds	Straphylococcus aureus 209P JC—1	Batilus subtilis ATCC 6633
B	1.56	0.78
C	1.56	0.78

Test Results 2

MIC (µg/ml)

Microorganisms / Test Compounds	Proteus mirabilis 1	Proteus mirabilis 18
A	0.05	<0.025
D	0.05	0.05
E	<0.025	<0.25
F	0.20	0.05
G	0.10	0.10
H	0.10	0.05

Test Results 3

MIC (μg/ml)

Microorganisms / Test Compounds	Proteus vulgaris 2
F	0.05
G	<0.025
H	<0.025

For therapeutic administration, the object compounds (I) and the pharmaceutically acceptable salts thereof of the present invention are used in the form of conventional pharmaceutical preparation which contains said compound, as active ingredients, in admixture with pharmaceutically acceptable carriers such as an organic or inorganic solid or liquid excipient which is suitable for oral, parenteral and external administration. The pharmaceutical preparations may be in solid form such as tablet, granule, powder, capsule, or liquid form such as solution, suspension syrup, emulsion and lemonade.

If needed, there may be included in the above preparation auxilliary substances, stabilizing agents, wetting agents and other commonly used additives such as lactose, magnesium stearate, terra alba, sucrose, corn starch, talc, stearic acid, gelatin, agar, pectin, peanut oil, olive oil, cacao butter and ethylene glycol.

While the dosage of the compounds (I) may vary from and also depend upon the age, conditions of the patient, a kind of diseases, a kind of the compounds (I) to be applied, etc. In general, amounts between 1 mg and about 4,000 mg or even more per day may be administered to a patient. An average single dose of about 50 mg, 100 mg, 250 mg, 500 mg, 1000 mg, 2000 mg of the object compounds (I) of the present invention may be used in treating diseases infected by pathogenic microorganisms.

The following examples are given for the purpose of illustrating the present invention.

Preparation of the starting compounds

Preparation 1

To a solution of N,N-dimethylformamide (8.8 g) and tetrahydrofuran (230 ml) was added dropwise phosphorus oxychloride (18.5 g) at −5 to 0°C, and the mixture was stirred for a while. To this solution was added 2-(2-formamidothiazol-4-yl)-2-methoxyiminoacetic acid (syn isomer) (25.2 g) at 3°C, followed by stirring at the same temperature for 40 minutes to prepare the activated acid solution.

On the other hand, a mixture of benzhydryl 7-amino-3-chloromethyl-3-cephem-4-carboxylate hydrochloride (45.1 g) and trimethylsilylacetamide (104.8 g) in ethyl acetate (400 ml) was stirred at ambient temperature for 20 minutes. To the resultant solution was added the activated acid solution prepared before at −40°C with stirring, and the stirring was continued at −30 to −10°C for 1.8 hours. After addition of water (200 ml), the organic layer was separated out. The remained aqueous solution was extracted with ethyl acetate, and this extract and the organic layer were combined and washed with a saturated aqueous solution of sodium bicarbonate and an aqueous solution of sodium chloride, followed by drying over anhydrous magnesium sulfate. After concentration, the precipitated substance was collected by filtration to give benzhydryl 7-[2-(2-formamidothiazol-4-yl)-2-methoxyiminoacetamido]-3-chloromethyl-3-cephem-4-carboxylate (syn isomer) (45.2 g). The filtrate was evaporated to dryness and the residue was washed with diethyl ether to recover the same product (7.9 g).

Total yield: 53.1 g.

I.R. (Nujol): 3250, 3160, 3110, 1780, 1720, 1690, 1660, 1630, 1565, 1540 cm^{-1}.

N.M.R. δ ppm (DMSO-d_6): 3.70 (2H, broad s), 3.93 (3H, s), 4.47 (2H, broad s), 5.30 (1H, d, J =5Hz), 6.03 (1H, dd, J=5Hz, 8Hz), 7.03 (1H, s), 7.17-7.73 (11H, m), 8.62 (1H, s), 9.90 (1H, d, J=8Hz).

Preparation 2

To a solution of benzhydryl 7-[2-(2-formamidothiazol-4-yl)-2-methoxyiminoacetamino]-3-chloromethyl-3-cephem-4-carboxylate (syn isomer)(25.0 g) in ethyl acetate (300 ml) was added a solution of triphenylphosphine (21.0 g) in tetrahydrofuran (170 ml), and the mixture was heated under reflux for 10 hours. The precipitated substance was collected by filtration to give [7-(2-(2-formamidothiazol-4-yl)-2-methoxyiminoacetamido)-4-benzhydryloxycarbonyl-3-cephem-3-yl-]methyl-triphenylphosphonium chloride (syn isomer) (17.7 g). The remained filtrate was heated under reflux for 10 hours. Similarly, the precipitated substance was collected by filtration to recover the same product (9.75 g). Further, this operation was repeated once to recover the same product (3.3 g).

Total yield: 30.75 g.

I. R. (Nujol): 1780, 1720, 1680, 1590, 1540 cm^{-1}.

Preparation 3

[7-(2-(2-Formamidothiazol-4-yl)-2-methoxyiminoacetamido)-4-benzhydryloxycarbonyl-3-cephem-3-yl]methyltriphenylphosphonium chloride (syn isomer) (5.33 g) was dissolved in a mixture of acetone (60 ml) and water (10 ml), and the solution was adjusted to pH 11 with 2N aqueous solution of sodium hydroxide, followed by extraction three times with ethyl acetate (100 ml). The extract was washed with an aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate and then evaporated to dryness to give a residue, which was pulverized with diethyl ether to obtain benzhydryl-7-[2-(2-formamidothiazol-4-yl)-2-methoxyiminoacetamido)-3-triphenylphosphoranylidenemethyl-3-cephem-4-carboxylate (syn isomer) (3.7 g).

I. R. (Nujol): 3300-3170, 1730, 1670, 1580, 1540 cm^{-1}.

Preparation 4

To a suspension of L-serine (50 g) in water (500 ml) and dioxane (500 ml) were added triethylamine (140 ml) and 2-tert-butoxycarbonyloxyimino-2-phenylacetonitrile (138 g), and the mixture was stirred at ambient temperature for 24 hours. After removal of the dioxane, the remained aqueous solution was adjusted to pH 8.0 with an aqueous sodium bicarbonate and then washed four times with ethyl acetate (200 ml). The aqueous solution was adjusted to pH 2.0 with conc. hydrochloric acid and then extracted twice with ethyl acetate (300 ml). The combined ethyl acetate solution was washed with an aqueous sodium chloride, dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. To the concentrate was added dropwise a solution of diazodiphenylmethane in ethyl acetate till the starting compound was disappeared on thin layer chromatography. Removal of the solvent gave a residue, which was pulverized with diisopropyl ether to obtain N-tert-butoxycarbonyl-L-serine benzhydryl ester (109 g).

I. R. (Nujol): 3250, 1746, 1677 cm^{-1}.

N.M.R. δ ppm (DMSO-d_6): 1.37 (9H, s), 3.73 (2H, t, J=12.0Hz), 4.20 (1H, m), 4.93 (1H, t, J=12Hz), 6.82 (1H, s), 7.40 (10H, broad s).

Preparation 5

A mixture of DL-homoserine (50 g), triethylamine (140 ml), 2-tert-butoxycarbonyloxyimino-2-phenylacetonitrile (103.3 g), water (500 ml) and dioxane (500 ml) was stirred at ambient temperature for 24 hours. After removal of the dioxane, the remained aqueous solution was adjusted to pH 8.5—9.0 with 10% aqueous sodium hydroxide and then washed with ethyl acetate (500 ml × 5). The resultant aqueous solution was adjusted to pH 2.0 with conc. hydrochloric acid and then extracted with ethyl acetate, followed by washing with an aqueous sodium chloride and drying over anhydrous magnesium sulfate. To this solution was added dropwise a solution of diazodiphenylmethane in ethyl acetate till the starting compound was disappeared on thin layer chromatography. Removal of the solvent gave a residue, which was pulverized with diisopropyl ether to obtain N-tert-butoxycarbonyl-DL-homoserine benzhydryl ester (117.0 g), mp 125—129°C.

I.R. (Nujol): 3500, 3320, 1735, 1687 cm^{-1}.

N.M.R δ ppm ($CDCl_3$): 1.43 (9H, s), 1.8—2.5 (2H, m), 3.6 (2H, m), 4.58 (1H, m), 5.5 (1H, d, J=8Hz), 6.92 (1H, s) 7.3 (10H, s).

Preparation 6

A solution of 7-(2-phenylacetamido)-3-vinyl-3-cephem-4-carboxylic acid (15.3 g), N-tert-butoxycarbonyl L-serine benzhydryl ester (15 g), triphenylphosphine (15.9 g) and diethyl diazenedicarboxylate (10.6 g) in tetrahydrofuran (450 ml) was heated under reflux for 3 hours. The reaction mixture was heated under reflux for 3 hours. The reaction mixture was concentrated under reduced pressure to give a residue, which was dissolved in ethyl acetate (30 ml), and washed with an aqueous sodium bicarbonate and an aqueous sodium chloride, followed by drying over anhydrous magnesium sulfate. Removal of the solvent gave a residue, which was chromatographed on silica gel (400 ml) eluting with methylene chloride, and fractions containing a desired compound were collected. Removal of the solvent gave a residue, which was pulverized with diisopropyl ether to obtain L-2-benzhydryloxycarbonyl-2-tert-butoxycarbonylaminoethyl 7-(2-phenylacetamido)-3-vinyl-3-cephem-4-carboxylate (17.2 g).

I.R (Nujol): 3350, 1767, 1735, 1718, 1678, 1635 cm^{-1}.

N.M.R δ ppm (DMSO-d_6): 1.40 (9H, s) 3.53, 4.00 (2H, ABq, J=18Hz), 3.57, (2H, s), 4.55 (3H, m), 5.13 (1H, d, J=5Hz), 5.35 (1H, d, J=11Hz), 5.61 (1H, dd, J=5Hz, 8Hz), 5.68 (1H, d, J=18Hz), 6.86 (1H, s), 6.92 (1H, dd, J=11Hz, 18Hz), 7.37 (5H, s), 7.57 (10H, broad s), 9.20 (1H, d, J=8Hz).

Preparation 7

A mixture of phosphorus pentachloride (4.5 g) pyridine (1.8 ml) and methylene chloride (50 ml) was stirred at ambient temperature for half an hour. To the resultant suspension was added L-2-benzhydryloxycarbonyl-2-tert-butoxycarbonylaminoethyl 7-(2-phenylacetamido)-3-vinyl-3-cephem-4-carboxylate (10 g) at 5°C, and the mixture was stirred at the same temperature for half an hour. After the reaction mixture was poured into methanol (60 ml) at −30°C, the mixture was stirred at −20°C for half an hour, followed by addition of water (50 ml), and then adjusting to pH 6.0 with 5% aqueous sodium hydroxide. After evaporation, the residue was extracted with methylene chloride. The extract was washed with an aqueous

sodium chloride and then dried over anhydrous magnesium sulfate, followed by treating with an activated charcoal. The filtrate was evaporated under reduced pressure, and thereto was added benzene, followed by azeotropically removing the pyridine by evaporation. The residue was pulverized with a mixed solvent of petroleum ether and diisopropyl ether to obtain L-2-benzhydryloxycarbonyl-2-tert-butoxycarbonyl-aminoethyl 7-amino-3-vinyl-3-cephem-4-carboxylate (7.5 g).

I.R. (Nujol): 3350, 1773, 1737, 1709, 1693 cm^{-1}.

N.M.R δ ppm (DMSO-d_6): 1.37 (9H, s), 3.47, 3.93 (2H, ABq, J=18Hz), 4.52 (3H, m), 4.68, 5.02 (2H, ABq, J=18Hz), 5.30 (1H, d, J=11Hz), 5.58 (1H, d, J=18Hz), 6.80, (1H, s), 6.82 (1H, dd, J=11Hz, 18Hz), 7.37 (10H, s).

Preparation 8

A suspension of (2-formamidothiazol-5-yl)glyoxylic acid (2.4 g) and methoxylamine hydrochloride (5.0 g) in water (144 ml) was adjusted to pH 4.9—5.0 with a saturated aqueous sodium bicarbonate and the mixture was stirred at ambient temperature for 4.7 hours. After water was added thereto in order to dissolve the insoluble material therein, the aqueous solution was concentrated to a volume of 100 ml. The precipitated material was collected by filtration, washed with water, followed by dissolving in a mixture of tetrahydrofuran and water. This solution was poured into a mixture of ethyl acetate and water, and the organic layer was separated out. After the aqueous solution was extracted with ethyl acetate, the combined ethyl acetate solution was washed with an aqueous sodium chloride and then dried over anhydrous magnesium sulfate. Removal of the solvent gave 2-(2-formamidothiazol-5-yl)-2-methoxyiminoacetic acid (anti isomer) (0.9 g), mp 159°C (dec.). The filtrate obtained above was further concentrated to a volume of 70 ml, and the precipitated material was collected by filtration to recover the same product (0.23 g). Total yield: 1,13 g.

I.R. (Nujol): 3180, 1700, 1560, 1460 cm^{-1}.

N.M.R. δ ppm (DMSO-d_6): 4.14 (3H, s), 8.30 (1H, s), 8.57 (1H, s).

Further to the filtrate was added ethyl acetate, and the mixture was adjusted to pH 1.5 with 10% hydrochloric acid, followed by separating out the ethyl acetate layer. After the remained aqueous solution was extracted with ethyl acetate, the combined ethyl acetate solution was washed with an aqueous sodium chloride and then dried over anhydrous magnesium sulfate. Removal of the solvent gave 2-(2-formamidothiazol-5-yl)-2-methoxyiminoacetic acid (syn isomer) (0.87 g), mp 183°C (dec.).

I.R. (Nujol): 1720, 1650, 1535, 1465 cm^{-1}.

N.M.R. δ ppm (DMSO-d_6): 3.92 (3H, s), 7.58 (1H, s), 8.57 (1H, s).

Preparation 9

To a solution of bromoacetyl bromide (20 g) in tetrahydrofuran (200 ml) were added N-tert-butoxycarbonyl-L-serine benzhydryl ester (10.84) and N,N-dimethylaniline (6.8 ml), and the mixture was stirred at 20 to 23°C for 80 minutes. After adjusting to pH 5.0 with 10% aqueous sodium hydroxide and 5% aqueous sodium bicarbonate, the tetrahydrofuran was removed by evaporation. The residue was dissolved in a mixture of ethyl acetate (200 ml) and water (100 ml), and then washed with 5% hydrochloric acid and an aqueous sodium chloride, followed by drying over anhydrous magnesium sulfate. Removal of the solvent gave a residue, which was pulverized with diisopropyl ether to obtain L-2-benzhydryloxycarbonyl-2-tert-butoxycarbonylaminoethyl 2-bromoacetate (21.3 g), mp 92—94°C.

I.R (Nujol): 3350, 1735, 1727, 1704, 1160 cm^{-1}.

N.M.R. δ ppm (DMSO-d_6): 1.40 (9H, s), 4.03 (2H, s), 4.67 (3H, m), 6.85 (1H, s), 7.37 (10H, s).

Preparation 10

A mixture of L-2-benzhydryloxycarbonyl-2-tert-butoxycarbonylaminoethyl 2-bromoacetate (20 g), N-hydroxyphthalimide (6.7 g), triethylamine (8.5 ml) and N,N-dimethylformamide (80 ml) was stirred at 10 to 15°C for half an hour. The reaction mixture was poured into 5% aqueous sodium chloride (1.5 l), and the precipitated material was collected by filtration and then washed with water, followed by dissolving in ethyl acetate (300 ml). The solution was washed twice with an aqueous sodium chloride and dried over anhydrous magnesium sulfate, followed by evaporation to give a residue, which was pulverized with diisopropyl ether to obtain L-2-benzhydryloxycarbonyl-2-tert-butoxycarbonylaminoethyl 2-phthalimidooxyacetate (24.5 g), mp 45—50°C.

I.R. (Nujol): 3420, 1740, 1720 (shoulder) cm^{-1}.

N.M.R. δ ppm (DMSO-d_6): 1.38 (9H, s), 4.55 (3H, broad s), 4.89 (2H, broad s), 6.93 (1H, s), 7.47 (10H, broad s), 8.00 (4H, s).

Preparation 11

To a solution of N-hydroxyphthalimide (4.3 g), N-tert-butoxycarbonyl-DL-homoserine benzhydryl ester (10 g) and triphenylphosphine in tetrahydrofuran (100 ml) was added dropwise a diethyl diazenedicarboxylate (4.6 g) at ambient temperature with stirring, and the stirring was continued at 32 to 35°C for 3 hours. Removal of the solvent gave a residue, which was chromatographed on silica gel eluting with a mixed solvent of benzene and acetone. Fractions containing a desired compound were collected and then

evaporated to obtain benzhydryl DL-2-tert-butoxycarbonylamino-4-phthalimidooxybutyrate (10 g), mp 162—163°C.

IR (Nujol): 3360, 1740, 1722, 1681 cm^{-1}.

NMR δ ppm ($CDCl_3$): 1.45 (9H, s), 2.37 (2H, q), J=6Hz), 4.26 (2H, t, J=6Hz), 4.58 (1H, m), 5.73 (1H, d, J=8Hz), 6.90 (1H, s), 7.3 (10H, s), 7.77 (4H, s).

Preparation 12

To a solution of L-2-benzhydryloxycarbonyl-2-tert-butoxycarbonylaminoethyl 2-phthalimidooxyacetate (20 g) in methylene chloride (100 ml) was added a solution of hydrazine monohydrate (3.5 g) in methanol under ice-cooling, and the mixture was stirred below 15°C for an hour. The precipitated material was collected by filtration and washed with methylene chloride. The washings and the above obtained methylene chloride solution were combined, adjusted to pH 7.0 with 5% hydrochloric acid, and washed with an aqueous sodium chloride, followed by drying over anhydrous magnesium sulfate. Removal of the solvent gave a residue, which was chromatographed on silica gel (200 ml) eluting with a mixed solvent of benzene and ethyl acetate, and fractions containing a desired compound were collected. Removal of the solvent gave a residue, which was pulverized with diisopropyl ether to obtain L-2-benzhydryloxycarbonyl-2-tert-butoxycarbonylaminoethyl 2-aminooxyacetate (10.5 g), mp 90—92°C.

IR (Nujol): 3400, 1745, 1720 cm^{-1}.

NMR δ ppm (DMSO-d_6): 1.38, (9H,s), 4.10 (2H, s), 4.45 (3H, broad s), 6.30 (2H, s), 6.84 (1H, s), 7.37 (10H, s).

Preparation 13

A solution of benzhydryl DL-2-tert-butoxycarbonylamino-4-phthalimidooxybutyrate (7.0 g) in methylene chloride (100 ml) was added dropwise to a solution of hydrazine monohydrate (2.0 g) in methanol (6 ml) at ambient temperature, and the mixture was stirred for half an hour. The precipitated material was collected by filtration and then washed with methylene chloride (30 ml). After the filtrate and washings were combined thereto was added water, followed by adjusting to pH 7.0 with conc. hydrochloric acid. The separated methylene chloride solution was washed with water and an aqueous sodium chloride, followed by drying over anhydrous magnesium sulfate. Removal of the solvent gave a residue which was pulverized with diisopropyl ether to obtain benzhydryl DL-2-tert-butoxycarbonylamino-4-aminooxybutyrate (5.0 g), mp 92—93°C.

IR (Nujol): 3340, 3305, 1730, 1695 cm^{-1}.

NMR δ ppm (DMSO-d_6): 1.38 (9H, s), 1.95 (2H, m), 3.58 (2H, t, J=6Hz), (1H, m), 5.92 (2H, s), 6.82 (1H, s) 7.37 (10H, s).

Preparation 14

To a suspension of (2-formamidothiazol-4-yl)-glyoxylic acid (3.6 g) in pyridine (3.7 ml) and water (33 ml) was added a solution of L-2-benzhydryloxycarbonyl-2-tert-butoxycarbonylaminoethyl 2-aminooxyacetate (10.5 g) in tetrahydrofuran (30 ml), and the mixture was stirred at ambient temperature for 5 hours. Water was added to the reaction mixture, followed by adjusting to pH 1.6 with conc. hydrochloric acid. After extraction with ethyl acetate, the extract was washed with an aqueous sodium chloride, and then dried over anhydrous magnesium sulfate. Removal of the solvent gave a residue, which was pulverized with diisopropyl ether to obtain 2-(2-formamidothiazol-4-yl)-2-(L-2-benzhydryloxycarbonyl-2-tert-butoxycarbonylaminoethoxycarbonyl-methoxyimino)acetic acid (syn isomer) (11.7 g), mp 110—113°C.

IR (Nujol): 3350, 3180, 1756 (shoulder), 1743, 1715, 1703 cm^{-1}.

NMR δ ppm (DMSO-d_6): 1.38 (9H, s), 4.47 (3H, broad s), 4.70 (2H, broad s), (1H, s), 7.40 (10H, broad s), 7.55 (1H, s), 8.55 (1H, s), 12.70 (1H, broad s).

Preparation 15

To a suspension of 2-(2-formamidothiazol-4-yl)-glyoxylic acid (3.40 g) in pyridine (3.6 ml) and water (32 ml) was added a solution of benzhydryl DL-2-tert-butoxycarbonylamino-4-aminooxybutyrate (7.0 g) in tetrahydrofuran (30 ml) at ambient temperature, and the mixture was stirred for 3 hours. The reaction mixture was poured into ethyl acetate (200 ml), and the separated ethyl acetate layer was washed with dilute hydrochloric acid and an aqueous sodium chloride, followed by drying over anhydrous magnesium sulfate. Removal of the solvent gave 2-(2-formamidothiazol-4-yl)-2-(DL-3-benzhydryloxycarbonyl-3-tert-butoxycarbonylaminopropoxyimino)acetic acid (syn isomer)(9.0 g), mp 61—65°C.

IR (Nujol): 3150, 1740, 1695 cm^{-1}.

NMR δ ppm (DMSO-d_6): 1.4 (9H, s), 2.1 (2H, m), 4.2 (3H, m), 6.82 (1H, s), 7.33 (10H, s), 7.53 (1H, s), 8.53 (1H, s).

Preparation 16

Vilsmeir reagent, which was prepared from N,N-dimethylformamide (0.48 g) and phosphorous oxychloride (1.0 g), was suspended in ethyl acetate (20 ml), and thereto was added 4-bromo-2-methoxyiminoacetoacetic acid (syn isomer) (1.34 g) under ice-cooling, followed by stirring at the same temperature for half an hour to prepare the activated acid solution. This solution was added to a solution of benzhydryl

7-amino-3-vinyl-3-cephem-4-carboxylate hydrochloride (2.15 g) and trimethylsilylacetamide (3.93 g) in ethyl acetate (30 ml) at −20°C, and the mixture was stirred at −20 to 0°C for 1.5 hours. To the reaction mixture were added ethyl acetate (100 ml) and water (100 ml), and the separated ethyl acetate solution was washed with a saturated aqueous sodium bicarbonate and an aqueous sodium chloride, followed by drying over anhydrous magnesium sulfate. Removal of the solvent gave a residue, which was washed with diethyl ether to obtain benzhydryl 7-(4-bromo-2-methoxyiminoacetoacetamido)-3-vinyl-3-cephem-4-carboxylate (syn isomer) (2.5 g).

IR (Nujol): 3280, 1770, 1710, 1700, 1660, 1600, 1560 cm^{-1}.

NMR δ ppm (DMSO-d_6): 3.78 (2H, q, J=18Hz), 4.07 (3H, s), 4.63 (2H, s), 5.27 (1H, d, J=5HZ), 5.30 (1H, d, J=11Hz), 5.63 (1H, d, J=17Hz), 5.93 (1H, dd, J=5Hz, 8Hz), 6.78 (1H, dd, J=11Hz), 17Hz), 6.98 (1H, s), 7.17—7.67 (10H, m), 9.57 (1H, d, J=8Hz).

Preparation 17

To a solution of benzhydryl 7-amino-3-vinyl-3-cephem-4-carboxylate hydrochloride (6.4 g) and trimethylsilylacetamide (9.8 g) in ethyl acetate (80 ml) was added 4-bromo-3,3-diethoxy-2-methoxyimino-butyryl chloride (syn isomer) (5.0 g) at −20°C with stirring, and the stirring was continued at −20 to −5°C for an hour. To the reaction mixture were added ethyl acetate and water, and the separated ethyl acetate solution was washed with a saturated aqueous sodium bicarbonate and an aqueous sodium chloride, followed by drying over anhydrous magnesium sulfate. Removal of the solvent gave benzhydryl 7-(4-bromo-3, 3-diethoxy-2-methoxyiminobutyramido)-3-vinyl-3-cephem-4-carboxylate (syn isomer) (10.1 g).

IR (Nujol): 1780, 1720, 1610, 1510 cm^{-1}.

NMR δ ppm (DMSO-d_6): 1.13 (3H, t, J=7Hz), 3.60 (2H, q, J=7Hz), 3.76 (2H, m), 3.83 (3H, s), 5.22 (1H, d, j=5Hz), 5.24 (1H, d, j=5Hz), 5.60 (1H, d, J=17Hz), 5.82 (1H, dd, J=5Hz, 8Hz), 6.70 (1H, dd, J=11Hz, 17Hz), 6.93 (1H, s), 7.17—7.60 (10H, m), 9.00 (1H, d, J=8Hz).

Preparation 18

To a solution of benzhydryl 7-(4-bromo-3,3-diethoxy-2-methoxyiminobutyramido)-3-vinyl-3-cephem-4-carboxylate (syn isomer) (6.5 g) in methylene chloride (60 ml) was added conc. hydrochloric acid (6 ml) at 3 to 5°C, and the mixture was stirred from under ice-cooling to at ambient temperature for 8 hours. After methylene chloride (100 ml) was added to the reaction mixture, it was washed with water and then dried over anhydrous magnesium sulfate. Removal of the solvent gave a residue, which was washed with diethyl ether to obtaine benzhydryl 7-(4-bromo-2-methoxyiminoacetoacetamido)-3-vinyl-3-cephem-4-carboxylate (syn isomer) (3.5 g).

IR (Nujol): 3280, 1770, 1710, 1700, 1660, 1600, 1560 cm^{-1}.

NMR δ ppm (DMSO-d_6): 3.78 (2H, q, J=18Hz), 4.07 (3H, s), 4.63 (2H, s), 5.27 (1H, d, J=5Hz), 5.30 (1H, d, J=11Hz), 5.63 (1H, d, J=17Hz), 5.93 (1H, dd, J=5Hz, 8Hz), 6.78 (1H, dd, J=11Hz, 17Hz), 6.98 (1H, s), 7.17—7.67 (10H, m), 9.57 (1H, d, J=8Hz).

Preparation 19

To a solution of benzhydryl 7-(4-bromo-3,3-diethoxy-2-methoxyiminobutyramido)-3-vinyl-3-cephem-4-carboxylate (syn isomer) (3.36 g) and anisole (2.1 g) in methylene chloride (20 ml) was added trifluoroacetic acid (8.0 g) under ice-cooling with stirring, and the stirring was continued at ambient temperature for an hour. After removal of the solvent, the residue was dissolved in a mixture of ethyl acetate and water. To the separated ethyl acetate solution was added water, followed by adjusting the pH 7 with a saturated aqueous sodium bicarbonate. To the separated aqueous solution was added ethyl acetate, followed by adjusting to pH 2 with 10% hydrochloric acid. The ethyl acetate layer was separated out, washed with an aqueous sodium chloride and then dried over anhydrous magnesium sulfate. Removal of the solvent gave 7-(4-bromo-2-methoxyiminoacetoacetamido)-3-vinyl-3-cephem-4-carboxylic acid (syn isomer) (1.6 g).

IR (Nujol): 3300,—3200, 1780, 1700, 1675 (shoulder), 1540 cm^{-1}.

Preparation 20

N-(2-Pyridylmethoxy)phthalimide (50 g) was suspended in ethanol (500 ml), and thereto was added hydrazine monohydrate (20.8 g) at 60°C, followed by stirring at the same temperature for an hour. To the reaction mixture was added conc. hydrochloric acid (60 ml) dissolved in water (450 ml) under cooling, and the precipitated materials were removed by filtration. The ethanol was removed by evaporation from the filtrate, and the precipitated materials therein were further removed by filtration. To the filtrate was added ethanol (500 ml) and then adjusted to pH 7.0 with 4N aqueous sodium hydroxide. Thereto was added (2-formamidothiazol-4-yl)glyoxylic acid (30.5 g), followed by adjusting to pH 4.5 with 10% hydrochloric acid and stirring for 1.5 hours. During the stirring, the pH value of the mixture was kept at 4 to 4.5 with 4N aqueous sodium hydroxide. After the reaction mixture was adjusted to pH 7.5 with 4N aqueous sodium hydroxide, the ethanol was removed by evaporation. The resultant aqueous solution was adjusted to pH 3.0 with 10% hydrochloric acid, and the precipitated crystals were collected by filtration to obtain 2-(2-formamidothiazol-4-yl)-2-(2-pyridylmethoxyimino)acetic acid (syn isomer) (35.4 g).

IR (Nujol): 3100, 1680, 1610, 1560, 1540 cm^{-1}.

NMR δ ppm ($NaHCO_3$+D_2O): 5.3 (2H, s), 7.47 (1H, s), 7.17—8.07 (3H, m), 8.47 (1H, s), 8.33—8.67 (1H, m).

Preparation 21

2-(2-Formamidothiazol-4-yl)-2-(3-pyridylmethoxyimino)-acetic acid (syn isomer) (8.0 g) was obtained by reacting (2-formamidothiazol-4-yl)glyoxylic acid (8.8 g) with 3-pyridylmethoxyamine, which was prepared from N-(3-pyridylmethoxy)phthalimide (14.5 g) and hydrazine monohydrate (6.3 g), according to a similar manner to that of Preparation 20.

IR (Nujol): 3400, 3050, 1670, 1550 cm^{-1}.

NMR δ ppm ($NaHCO_3+D_2O$): 5.28 (2H, s), 7.44 (1H, s), 7.24—7.50 (1H, m), 7.82 (1H, m), 8.46 (1H, s), 8.14—8.66 (2H, m).

Preparation 22

2-(2-Formamidothiazol-4-yl)-2-(4-pyrodylmethoxyimino)-acetic acid (syn isomer) (10.5 g) was obtained by reacting (2-formamidothiazol-4-yl)glyoxylic acid (10.3 g) with 4-pyridylmethoxyamine, which was prepared from N-(4-pyridylmethoxy)phthalimide (17.0 g) and hydrazine monohydrate (6.0 g), according to a similar manner to that of Preparation 20.

IR (Nujol): 3500, 1650, 1560, 1500 cm^{-1}.

NMR δ ppm ($NaHCO_3+D_2O$): 5.22 (2H, s), 7.38 (1H, s), 7.27—7.47 (2H, m), 8.42 (1H, s), 8.33—8.55 (2H, m).

Preparation 23

To a solution of sodium 7 - (5 - amino - 5 - carboxypentanamido) - 3 - hydroxymethyl - 3 - cephem - 4 - carboxylate (118.6 g) in water (1000 ml) and acetone (600 ml) was added dropwise benzoyl chloride (42.1 g) under ice-cooling with stirring at 10°C while the reaction mixture was continually adjusted to pH 6.5 to 7.5 with 20% aqueous sodium carbonate. After the stirring was continued at the same temperature for an hour, the reaction mixture was adjusted to pH 6.0 with conc. hydrochloric acid, followed by removing the acetone and washing with ethyl acetate (500 ml). To this aqueous solution was added ethyl acetate (300 ml), and thereto was added a solution of diphenyldiazomethane in ethyl acetate till the starting compound was disappeared on a thin layer chromatography, followed by adjusting to pH 3.0 with conc. hydrochloric acid. The ethyl acetate layer was separated, washed with an aqueous sodium chloride and then dried over magnesium sulfate, followed by evaporation under reduced pressure. After the residue was dissolved in acetone (400 ml), the solution was added dropwise to diisopropyl ether (4000 ml). The precipitated crystals were collected by filtration and then dried to obtain benzhydryl 7 - (5 - benzamido - 5 - benzhydryloxycarbonylpentanamido) - 3 - hydroxymethyl - 3 - cephem - 4 - carboxylate (224.8 g), mp 100—110°C.

I.R. (Nujol): 3270, 1770, 1730, 1660, 1640 cm^{-1}.

NMR δ ppm (DMSO-d_6): 1.3—2.7 (6H, m), 3.38 (1H, s), 3.63 (2H, m), 4.27 (2H, d, J=5Hz), 4.67 (1H, m), 5.15 (1H, d, J=5Hz), 5.77 (1H, dd, J=5Hz, 8Hz), 6.87 (1H, s), 6.95 (1H, s), 7.43 (25H, m), 7.97 (1H, m), 8.87 (1H, m).

Preparation 24

To a solution of benzhydryl 7 - (5 - benzamido - 5 - benzhydryloxycarbonylpentanamido) - 3 - hydroxymethyl - 3 - cephem - 4 - carboxylate (100 g) in methylene chloride (600 ml) was added at a time phosphorus pentachloride (25.6 g) at −30°C, followed by adding dropwise pyridine (9.8 g) at the same temperature. After the reaction mixture was stirred at −20°C for an hour, it was poured into a mixture of methylene chloride (500 ml) and water (300 ml). The separated organic layer was washed with an aqueous sodium chloride, dried over magnesium sulfate and then evaporated to dryness to obtain benzhydryl 7 - (5 - benzamido - 5 - benzhydryloxycarbonylpentanamido) - 3 - chloromethyl - 3 - cephem - 4 - carboxylate (114.5 g), mp 90—110°C (dec.).

I.R. (Nujol): 1780, 1725, 1640 cm^{-1}.

NMR δ ppm (DMSO-d_6): 1.3—2.5 (6H, m), 3.67 (2H, m), 4.43 (2H, m), 4.67 (1H, m), 5.22 (1H, d, J=5Hz), 5.83 (1H, m), 6.83 (1H, s), 7.00 (1H, s), 7.4 (25H, m), 7.92 (1H, m) 8.90 (1H, m).

Preparation 25

To a solution of benzhydryl 7 - (5 - benzamido - 5 - benzhydryloxycarbonylpentanamido) - 3 - chloromethyl - 3 - cephem - 4 - carboxylate (102 g) in N,N-dimethylformamide (150 ml) were added triphenylphosphine (48.5 g) and sodium iodide (18.4 g), and the mixture was stirred at ambient temperature for 1.5 hours. The reaction mixture was added dropwise to isopropyl alcohol (5000 ml), and the precipitated material was collected by filtration and washed with diisopropyl ether to obtain [7 - (5 - benzamido - 5 - benzhydryloxycarbonylpentanamido) - 4 - benzhydryloxycarbonyl - 3 - cephem - 3 - yl]methyl-triphenylphosphonium iodide (123.5 g), mp 165—175°C (dec.).

I.R. (Nujol): 1780, 1730, 1710, 1650 cm^{-1}.

NMR δ ppm (DMSO-d_6): 1.3—2.6 (6H, m), 4.33 (2H, m), 4.67 (2H, m), 5.13 (1H, m), 5.33 (1H, d, J=5Hz), 5.75 (1H, m), 6.33 (1H, s), 6.83 (1H, s), 7.0—8.3 (41H, m), 8.92 (1H, m).

Preparation 26

To a solution of [7 - (5 - benzamido - 5 - benzhydryloxycarbonylpentanamido) - 4 - benzhydryloxycarbonyl - 3 - cephem - 3 - yl]methyltriphenyl - phosphonium iodide (123.5 g) in methylene chloride (1000 ml) was added 36% aqueous formaldehyde (300 ml), followed by adjusting to pH 9.0 with 20%

aqueous sodium bicarbonate. After the mixture was stirred at 25°C for 2 hours, it was adjusted to pH 5.0 with conc. hydrochloric acid. The separated organic solution was concentrated, and to the concentrate was added ethyl acetate. The precipitated crystals were collected by filtration and then dried to obtain benzhydryl 7 - (5 - benzamido - 5 - benzhydryloxycarbonylpentanamido) - 3 - vinyl - 3 - cephem - 4 - carboxylate (63.5 g), mp 180—184°C (dec.).

I.R. (Nujol): 3300, 1770, 1730, 1710, 1650 cm^{-1}.

NMR δ ppm (DMSO-d_6): 1.3—2.6 (6H, m), 3.72 (2H, m), 4.67 (1H, m), 5.1—5.6 (2H, m), 5.7—5.9 (2H, m), 6.83 (1H, dd, J=12Hz, 18Hz), 6.86 (1H, s), 7.0 (1H, s), 7.42 (25H, m), 7.98 (1H, m), 8.92 (1H, m).

Preparation 27

To a suspension of phosphorus pentachloride (15.5 g) in methylene chloride (200 ml) was added dropwise pyridine (5.9 g) at 5 to 10°C with stirring, and the stirring was continued at 5°C for 20 minutes. Thereto was added at a time benzhydryl 7 - (5 - benzamido - 5 - benzhydryloxycarbonylpentanamido) - 3 - vinyl - 3 - cephem - 4 - carboxylate (20 g) at 5°C, and the mixture was stirred at the same temperature for 2 hours. To the reaction mixture was added gradually methanol (120 ml) at −40°C, followed by stirring at −20 to −10°C for an hour. Removal of the solvent gave a residue, to which ethyl acetate (300 ml) and water (50 ml) were added. The mixture was stirred under ice-cooling for a while, and the precipitated crystals were collected by filtration and then washed with isopropyl alcohol to obtain benzhydryl 7 - amino - 3 - vinyl - 3 - cephem - 4 - carboxylate hydrochloride (8.4 g), mp 180—195°C (dec.).

I.R. (Nujol): 1760, 1705, 1580 cm^{-1}.

NMR δ ppm (DMSO-d_6): 3.88 (2H, q, J=18Hz), 5.1—5.4 (2H, m), 5.58 (1H, d, J=6Hz), 5.93 (1H, m), 6.97 (1H, s), 7.0 (1H, dd, J=12Hz, 18Hz), 7.42 (10H, m), 9.17 (2H, m).

Preparation 28

To a suspension of benzhydryl 7 - amino - 3 - vinyl - 3 - cephem - 4 - carboxylate hydrochloride (48 g) in methanol (250 ml) and anisole (70 ml) was added p-toluenesulfonic acid (85 g), and the mixture was stirred at 50°C for 2 hours. The reaction mixture was poured into 10% aqueous sodium carbonate (600 ml) and ethyl acetate (700 ml), followed by adjusting to pH 7.5 with 20% aqueous sodium carbonate. The separated aqueous solution was washed with ethyl acetate (500 ml) and then adjusted to pH 2.5 with conc. hydrochloric acid, followed by stirring under ice-cooling for an hour. The precipitated crystals were collected by filtration and washed with acetone to obtain 7 - amino - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (15.4 g), mp 200 to 230°C (dec.).

I.R. (Nujol): 1800, 1605 cm^{-1}.

NMR δ ppm (D_2O + $NaHCO_3$): 3.67 (2H, s), 4.8—5.8 (5H, m), 6.88 (1H, dd, J=12Hz, 18Hz).

Preparation 29

To a suspension of phosphorus pentachloride (27.0 g) in methylene chloride (200 ml) was added dropwise pyridine (10.3 g) at 0°C, followed by stirring at 5°C for 20 minutes. Thereto was added at a time benzhydryl 7 - (5 - benzamido - 5 - benzhydryloxycarbonylpentanamido) - 3 - hydroxymethyl - 3 - cephem - 4 - carboxylate (21.0 g) at −40°C, followed by stirring at −30°C for an hour and at −10°C for additional an hour. To the reaction mixture was added at a time at −40°C methanol (100 ml), which was pre-cooled to −40°C, followed by stirring at −10°C for an hour. Removal of the solvent gave a residue, to which methylene chloride (100 ml), water (30 ml) and diisopropyl ether (100 ml) were added in turn, and the mixture was stirred under ice-cooling for a while. The precipitated crystals were collected by filtration and suspended in ethyl acetate (300 ml), followed by adjusting to pH 8.0 with an aqueous sodium bicarbonate. The separated organic solution was washed with an aqueous sodium chloride and then dried over magnesium sulfate. Removal of the solvent gave benzhydryl 7 - amino - 3 - chloromethyl - 3 - cephem - 4 - carboxylate (2.8 g), mp 135—140°C (dec.).

I.R. (Nujol): 3400, 1760, 1725, 1650 cm^{-1}.

NMR δ ppm (DMSO-d_6): 3.60 (2H, q, J=17Hz), 4.38 (2H, s), 4.85 (1H, d, J=5Hz), 5.05 (1H, d, J=5Hz), 6.95 (1H, s), 7.4 (10H, m), 8.8 (2H, m).

Preparation 30

To a solution of benzhydryl 7 - amino - 3 - chloromethyl - 3 - cephem - 4 - carboxylate (8.0 g) in N,N-dimethylformamide (40 ml) were added molecular sieve (10 g) and benzaldehyde (2.1 g), followed by stirring at 40°C for 40 minutes. Thereto were added sodium iodide (2.9 g) and triphenylphosphine (10.1 g), followed by stirring at 40°C for an hour. The reaction mixture was added dropwise to a mixture of diisopropyl ether (200 ml) and ethyl acetate (100 ml), and the precipitated crystals were collected by filtration and then dried to obtain [4 - benzhydryloxycarbonyl - 7 - benzylideneamino - 3 - cephem - 3 - yl]methyl - triphenyl - phosphonium iodide (16.9 g), mp 150—158°C (dec.).

I.R. (Nujol): 1780, 1705, 1635 cm^{-1}.

NMR δ ppm (DMSO-d_6): 3.67 (2H, m), 5.2 (2H, m), 5.58 (1H, d, J=5Hz), 5.82 (1H, d, J=5Hz), 6.30 (1H, s), 7.2—8.3 (30H, m), 8.70 (1H, s).

Preparation 31

To a solution of [4 - benzhydryloxycarbonyl - 7 - benzylidene - amino - 3 - cephem - 3 - yl]methyl - triphenylphosphonium iodide (16.9 g) in methylene chloride (200 ml) and water (100 ml) was added 36% aqueous formaldehyde (48 ml), followed by adjusting to pH 9.0 with sodium carbonate. After the mixture was stirred at ambient temperature for an hour, the separated organic solution was washed with an aqueous sodium chloride and then dried over magnesium sulfate. Removal of the solvent gave benzhydryl 7 - benzylideneamino - 3 - vinyl - 3 - cephem - 4 - carboxylate (8.6 g), mp 124—132°C.

I.R. (Nujol): 1770, 1710, 1630 cm^{-1}.

NMR δ ppm (DMSO-d_6): 3.75 (2H, q, J=18Hz), 5.1—5.8 (4H, m), 6.75 (1H, dd, J=10Hz, 18Hz), 6.93 (1H, s), 7.1—8.0 (15H, m), 8.58 (1H, s).

Preparation 32

To a suspension of benzhydryl 7 - benzylideneamino - 3 - vinyl - 3 - cephem - 4 - carboxylate (8.6 g) in anisole (10 ml) was added dropwise trifluoroacetic acid (10 ml) at −20°C, and the reaction temperature was gradually raised to ambient temperature with stirring, followed by stirring at ambient temperature for half an hour. The reaction mixture was poured into a mixture of ethyl acetate (100 ml) and a saturated aqueous sodium bicarbonate (100 ml), and then the mixture was adjusted to pH 7.5 with 20% aqueous sodium carbonate. The separated aqueous solution was washed with ethyl acetate (100 ml) and adjusted to pH 7.2 with conc. hydrochloric acid, followed by subjecting to column chromatography on alumina (10 ml). Elution was carried out with 15% aqueous sodium chloride, and fractions containing a desired compound were collected and then adjusted to pH 3.3 with conc. hydrochloric acid. The precipitated crystals were collected by filtration, washed with acetone and dried to obtain 7 - amino - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (2.0 g), mp 200—230°C (dec.).

I.R. (Nujol): 1800, 1605 cm^{-1}.

NMR δ ppm (D_2O+$NaHCO_3$): 3.67 (2H, s), 4.8—5.8 (5H, m), 6.88 (1H, dd, J=12Hz, 18Hz).

Preparation 33

To a solution of N-hydroxyphthalimide (70.08 g) in acetonitrile (300 ml) were added triethylamine (48 g) and tert-butyl 4-bromocrotonate (96.0 g) with stirring, and the mixture was refluxed under heating for 1.5 hours. The reaction mixture was poured into water (600 ml), followed by extraction with ethyl acetate. The extract was washed with a saturated aqueous sodium chloride, dried over magnesium sulfate and then evaporated to dryness under reduced pressure to give a residue, which was pulverized with n-hexane. The resultant substance was subjected to column chromatography on silica gel eluting with a mixed solvent of n-hexane, ethyl acetate and diisopropyl ether (5;0.5:4.5 by volume), and the fractions containing a desired compound were collected. Removal of the solvent gave a residue, which was pulverized with n-hexane and collected by filtration to obtain tert-butyl 4-phthalimidooxycrotonate (41.7 g).

NMR δ ppm (DMSO-d_6): 1.45 (9H, s), 4.90 (2H, m), 6.09 (1H, m), 6.66—7.19 (1H, m), 7.86 (4H, s).

Preparation 34

To a solution of tert-butyl 4-phthalimidooxycrotonate (20.0 g) in methylene chloride (140 ml) was added a solution of hydrazine monohydrate (5.0 g) in methanol (10 ml) with stirring, and the stirring was continued at ambient temperature for 15 minutes. The insoluble substance was collected by filtration and washed with methylene chloride. The washings and the filtrate were combined and then extracted three times with 5% hydrochloric acid. After the combined extracts were washed with diethyl ether, thereto was added methylene chloride, followed by adjusting to pH 7.5 with 28% aqueous ammonium hydroxide. The separated methylene chloride solution was washed with a saturated aqueous sodium chloride and then dried over magnesium sulfate. Removal of the solvent gave an oil of tert-butyl 4-aminooxycrotonate (11.03 g).

I.R. (Film): 3340, 3250, 2980, 2940, 1720, 1660 cm^{-1}.

NMR δ ppm (DMSO-d_6): 1.43 (9H, s), 4.18 (2H, m), 5.85 (1H, m), 6.14 (2H, broad s), 6.52—7.06 (1H, m).

Preparation 35

To tert-butyl 4-aminooxycrotonate (10.0 g) were added ethanol (150 ml) and water (150 ml), followed by gradually adding (2-formamidothiazol-4-yl)glyoxylic acid (11.0 g) with stirring. During the addition, the mixture was adjusted to pH 5 to 5.5 with 10% aqueous sodium hydroxide, and the stirring was continued at ambient temperature for 2 hours. After removal of the ethanol, to the remaining aqueous solution was added ethyl acetate, followed by adjusting to pH 7.5 with 10% aqueous sodium hydroxide. The aqueous layer was separated and washed with ethyl acetate. Thereto was further added ethyl acetate, followed by adjusting to pH 2.0 with 10% hydrochloric acid. The separated organic layer was washed with a saturated aqueous sodium chloride and then dried over magnesium sulfate. Removal of the solvent gave a residue, which was pulverized with n-hexane and tetrahydrofuran, and collected by filtration. To this substance were added ethanol (50 ml) and water (30 ml), followed by adjusting to pH 7.5 with 10% aqueous sodium hydroxide. The precipitated substance was collected by filtration, washed with a mixture solvent of water and ethanol (1:1 by volume), followed by addition of water and ethyl acetate, and adjusting to pH 2.0 with 10% hydrochloric acid. The organic layer was separated, washed with a saturated aqueous sodium

chloride and then dried over magnesium sulfate. Removal of the solvent gave a residue, which was pulverized with n-hexane and tetrahydrofuran to obtain 2 - (trans - 3 - tert - butoxycarbonylallyloxyimino) - 2 - (2 - formamidothiazol - 4 - yl)acetic acid (syn isomer) (12.01 g).

I.R. (Nujol): 3150, 1720, 1650 cm^{-1}.

NMR δ ppm (DMSO-d_6): 1.47 (9H, s), 4.89 (2H, m), 5.96 (1H, m), 6.69—7.16 (1H, m), 7.60 (1H, s), 8.57 (1H, s), 12.72 (1H, broad s).

Preparation 36

To a solution of 2 - (trans - 3 - tert - butoxycarbonylallyloxyimino) - 2 - (2 - formamidothiazol - 4 - yl)acetic acid (syn isomer) (8.0 g) in ethyl acetate (60 ml) and ethanol (60 ml) was added 10% palladium on carbon (4.0 g) moistened in water (3 ml) in a stream of nitrogen atmosphere, followed by subjecting to catalytic reduction under atmospheric pressure for 4 hours. After the catalyst was removed by filtration, the filtrate was evaporated. To the residue were added water and ethyl acetate, followed by adjusting to pH 7.5 with a saturated aqueous sodium bicarbonate. The separated aqueous layer was washed with ethyl acetate, and thereto was added ethyl acetate, followed by adjusting to pH 2.0 with 10% hydrochloric acid. The separated organic layer was washed with a saturated aqueous sodium chloride and then dried over magnesium sulfate. Removal of the solvent gave a residue, which was crystallized from n-hexane and collected by filtration to obtain 2 - (3 - tert - butoxycarbonylpropoxyimino) - 2 - (2 - formamidothiazol - 4 - yl)acetic acid (syn isomer) (1.80 g).

NMR δ ppm (DMSO-d_6): 1.44 (9H, s), 1.93 (2H, m), 2.33 (2H, t, J=6.0Hz), 4.20 (2H, t, J=6.0Hz), 7.61 (1H, s), 8.61 (1H, s), 12.63 (1H, broad s).

Preparation 37

Ethyl (2 - formamido - 5 - chlorothiazol - 4 - yl)glyoxylate (14.5 g) was added to a solution of 1N aqueous potassium hydroxide (110 ml) at ambient temperature, and the mixture was stirred for 10 minutes to prepare the solution of potassium (2 - formamido - 5 - chlorothiazol - 4 - yl)glyoxylate. After this solution was adjusted to pH 2 with 10% hydrochloric acid under ice-cooling, thereto were added pyridine (20 ml) and a solution of tert-butyl 2-aminooxyacetate (10.3 g) in tetrahydrofuran (50 ml), followed by stirring at ambient temperature for 5 hours. After the reaction mixture was washed with ethyl acetate, the remaining aqueous solution was adjusted to pH 1.5 with 10% hydrochloric acid and extracted with ethyl acetate. The extract was washed with an aqueous sodium chloride and then dried over magnesium sulfate. Removal of the solvent gave 2 - tert - butoxycarbonylmethoxyimino - 2 - (2 - formamido - 5 - chlorothiazol - 4 - yl)acetic acid (syn isomer) (8.5 g).

I.R. (Nujol): 3150, 1725, 1690, 1650, 1560, 1530 cm^{-1}.

NMR δ ppm (DMSO-d_6): 1.47 (9H, s), 4.75 (2H, s), 8.7 (1H, s), 12.8 (1H, s).

Preparation 38

a) 1N Aqueous sodium hydroxide (49 ml) was added to a suspension of S-methyl (6 - formamidopyridin - 2 - yl)thioglyoxylate (10 g) in methanol (100 ml), and the mixture was stirred at ambient temperature for 50 minutes to prepare the solution of sodium (6 - formamidopyridin - 2 - yl)-glyoxylate. To this solution was added tert-butyl 2 - aminooxyacetate (7.2 g) and the mixture was adjusted to pH 3 to 4 with 6N hydrochloric acid, followed by stirring at ambient temperature for 4 hours. The reaction mixture was neutralized with an aqueous sodium bicarbonate and concentrated to half of the original volume under reduced pressure, followed by washing with ethyl acetate and adjusting to pH 1.5 with 10% hydrochloric acid.

The resultant aqueous solution was extracted three times with ethyl acetate, and the combined extracts were washed with a saturated aqueous sodium chloride and dried over magnesium sulfate. Removal of the solvent gave 2 - tert - butoxycarbonylmethoxyimino - 2 - (6 - formamidopyridin - 2 - yl)-acetic acid (syn isomer) (11.9 g), mp 162—168°C.

I.R. (Nujol): 3180, 1741, 1673 cm^{-1}.

NMR δ ppm (DMSO-d_6): 1.47 (9H, s), 4.73 (2H, s), 7.3—8.3 (3H, m), 9.17 (1H, broad s), 10.7 (1H, d, J=6Hz).

b) 2 - (5 - Amino - 1,2,4 - thiadiazol - 3 - yl) - 2 - tert - butoxycarbonylmethoxyiminoacetic acid (syn isomer), mp 150—155°C (dec.), was obtained by reacting S-methyl (5 - formamido - 1,2,4 - thiadiazol - 3 - yl)thioglyoxylate with aqueous sodium hydroxide and then tert-butyl 2 - aminooxyacetate according to a similar manner to that of part a).

I.R. (Nujol): 3420, 3230, 3100, 1725, 1610, 1530 cm^{-1}.

NMR δ ppm (DMSO-d_6): 1.45 (9H, s), 4.70 (2H, s), 8.12 (2H, broad s).

Preparation 39

Vilsmeier reagent was prepared from phosphorus oxychloride (14.8 g) and N,N - dimethylformamide (7.07 g) in ethyl acetate (50 ml) in a conventional manner. 2 - (tert - Butoxycarbonylmethoxyimino) - 2 - (formamidothiazol - 4 - yl)acetic acid (syn isomer) (29 g) was added to the stirred suspension of Vilsmeier reagent in ethyl acetate (250 ml) under ice-cooling and stirred for 30 minutes at same temperature to

prepare an activated acid solution. On the other hand, benzhydryl 7 - amino - 3 - chloromethyl - 3 - cephem - 4 - carboxylate monohydrochloride (36.1 g) was dissolved in a solution of trimethylsilylacetamide (63 g) in ethyl acetate (400 ml). To this solution was added the above activated acid solution at −12°C and the mixture was stirred for an hour at −20 to 0°C. Water was added to the reaction mixture at 0°C. The organic layer was separated, washed with a saturated aqueous sodium bicarbonate and an aqueous sodium chloride. The solution was dried over magnesium sulfate and evaporated under reduced pressure. The residue was pulverized with diethyl ether to give benzhydryl 7 - [2 - tert - butoxycarbonylmethoxyimino - 2 - (2 - formamidothiazol - 4 - yl)acetamido] - 3 - chloromethyl - 3 - cephem - 4 - carboxylate (syn isomer) (49.7 g).

I.R. (Nujol): 3200, 1780, 1720, 1680, 1540 cm^{-1}.

NMR δ ppm (DMSO-d_6): 1.42 (9H, s), 3.66 (2H, q, J=18Hz), 4.43 (2H, s), 4.64 (2H, s), 5.27 (1H, d, J=5Hz), 5.98 (1H, d d, J=5Hz, 8Hz), 6.96 (1H, s), 7.00—7.60 (11H, m), 8.50 (1H, s), 9.64 (1H, d, J=8Hz), 12.58 (1H, broad s).

Preparation 40

Sodium iodide (4.5 g) was added to a solution of benzhydryl 7 - [2 - tert - butoxycarbonylmethoxyimino - 2 - (2 - formamidothiazol - 4 - yl)acetamido] - 3 - chloromethyl - 3 - cephem - 4 - carboxylate (7.6 g) in acetone (70 ml) and the mixture was stirred for 2.5 hours at ambient temperature. The reaction mixture was poured into a mixture of ethyl acetate (200 ml) and an aqueous sodium chloride (100 ml), and the organic layer was separated out, washed with 10% aqueous sodium thiosulfate and an aqueous sodium chloride. The solution was dried over magnesium sulfate and evaporated to give a residue. This residue and triphenylphosphine (5.2 g) were dissolved in ethyl acetate (100 ml) and stirred for an hour. The precipitates were collected by filtration, washed with ethyl acetate and dried to give [4 - benzhydryloxycarbonyl - {7 - (2 - tert - butoxycarbonylmethoxyimino) - 2 - (2 - formamidothiazol - 4 - yl)-acetamido} - 3 - cephem - 3 - ylmethyl] - triphenyl - phosphonium iodide (6.5 g).

I.R. (Nujol): 1785, 1710, 1680, 1530 cm^{-1}.

Preparation 41

A solution of ethyl 3 - amino - 3 - thioxopropionate (73.5 g) in diethyl ether (100 ml) was added to a solution of bromopiruvic acid (88.5 g) in diethyl ether (300 ml) and stirred for 15 hours at ambient temperature. The precipitates were collected by filtration and added to a mixture of water (500 ml) and diethyl ether (300 ml) and then adjusted to pH 7.5 with 20% aqueous sodium carbonate. The separated aqueous solution was adjusted to pH 1.0 with conc. hydrochloric acid and extracted with diethyl ether. The diethyl ether layer was dried over magnesium sulfate and evaporated. The residue was washed with diisopropyl ether to give ethyl 2 - (4 - carboxythiazol - 2 - yl)acetate (57.1 g).

I.R. (Nujol): 3100, 2870—2400, 1730, 1670 cm^{-1}.

NMR δ ppm (DMSO-d_6): 1.28 (3H, t, J=7Hz), 4.23 (2H, q, J=7Hz), 4.30 (2H, s), 8.50 (1H, s).

Preparation 42

Triethylamine (10.1 g) was added to a solution of ethyl 2 - (4 - carboxythiazol - 2 - yl)acetate (21.5 g) in tert-butanol (200 ml) and diphenylphosphorous azide (27.5 g) and the mixture was refluxed and stirred for 2 hours. After removing the solvent from the reaction mixture, the residue was dissolved in ethyl acetate (500 ml). The ethyl acetate was washed with water, a saturated aqueous sodium bicarbonate and an aqueous sodium chloride, and then dried over magnesium sulfate. The solvent was removed by evaporation, and the residue was washed with diisopropyl ether and collected by filtration to give ethyl 2 - (4 - tert - butoxycarbonylaminothiazol - 2 - yl)acetate (19.1 g).

I.R. (Nujol): 3180, 1730, 1710, 1530 cm^{-1}.

NMR δ ppm (DMSO-d_6): 1.23 (3lH, t, J=7Hz), 1.50 (9H, s), 4.07 (2H, s), 4.15 (2H, q, J=7Hz), 7.15 (1H, s), 10.00 (1H, s).

Preparation 43

Ethyl 2 - (4 - tert - butoxycarbonylaminothiazol - 2 - yl)acetate (5.1 g) was added to a solution of selenium dioxide (2.96 g) in dioxane (60 ml) and water (2 ml) at 110°C and stirred for 4.5 hours at 110°C. The mixture was evaporated and the residue was dissolved in ethyl acetate and water. The separated ethyl acetate layer was washed with an aqueous sodium chloride and dried over magnesium sulfate. After removing the solvent, the residue was subjected to column chromatography on silica gel and eluted with methylene chloride. The fraction containing an object compound was evaporated to give ethyl (4 - tert - butoxycarbonylaminothiazol - 2 - yl)glyoxylate (4.2 g).

I.R. (Film): 3250, 3150, 1720, 1680 cm^{-1}.

NMR δ ppm ($CDCl_3$): 1.42 (3H, t, J=7Hz), 1.52 (9H, s), 4.44 (2H, q, J=7Hz), 7.89 (1H, s), 8.28 (1H, s).

Preparation 44

A solution of sodium hydroxide (2.05 g) in water (30 ml) was added to a solution of ethyl (4 - tert - butoxycarbonylaminothiazol - 2 - yl)glyoxylate (7.7 g) in methanol (20 ml) and stirred for 1 hour at ambient temperature. The mixture was adjusted to pH 7.0 with 10% hydrochloric acid and washed with diethyl

ether. The separated aqueous layer was adjusted to pH 2.0 with 10% hydrochloric acid and extracted with diethyl ether. The diethyl ether layer was washed with an aqueous sodium chloride and dried over magnesium sulfate. The solvent was removed by evaporation, and the resultant (4 - tert-butoxycarbonyl-aminothiazol - 2 - yl)glyoxylic acid was dissolved in methanol (20 ml). On the other hand, a solution of 1N-sodium methylate in methanol (25 ml) was added to a solution of methoxylamine hydrochloride (2.35 g) in methanol (20 ml) and phenolphtharain indicator (2—3 drops), and stirred for 30 minutes. The insoluble material was filtered off, and the filtrate was added to the above solution and stirred for 2 hours at ambient temperature. The diisopropyl ether was added to the reaction mixture and the precipitates were collected by filtration to give 2 - methoxyimino - 2 - (4 - tert - butoxycarbonylaminothiazol - 2 - yl)acetic acid (syn isomer) (3.6 g).

I.R. (Nujol): 3250, 3150, 1730, 1640, 1630 cm^{-1}.

NMR δ ppm (DMSO-d_6): 1.45 (9H, s), 3.97 (3H, s), 7.37 (1H, s), 10.33 (1H, s).

Preparation 45

Benzhydryl 7 - [(2 - formamidothiazol - 4 - yl)glyoxylamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (6.1 g) was obtained by reacting benzhydryl 7 - amino - 3 - vinyl - 3 - cephem - 4 - carboxylate hydrochloride (6.0 g) with (2 - formamidothiazol - 4 - yl)glyoxylic acid (3.93 g) according to the similar manner to that of Example 1, mp 141—144°C (dec.).

I.R. (Nujol): 3150, 1780, 1720, 1695, 1670, 1620, 1520 cm^{-1}.

NMR δ ppm (DMSO-d_6): 3.78 (2H, q, J=18Hz), 5.33 (1H, d, J=5Hz), 5.33 (1H, d, J=11Hz), 5.68 (1H, d, J=17Hz), 5.93 (1H, dd, J=5Hz, 8Hz), 6.87 (1H, dd, J=11Hz, 17Hz), 7.00 (1H, s), 7.20—7.67 (10H, m), 8.50 (1H, s), 8.63 (1H, s), 9.97 (1H, d, J=8Hz), 12.82 (1H, broad s).

Preparation 46

7 - [(2 - Formamidothiazol - 4 - yl)glyoxylamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (3.0 g) was obtained by reacting benzhydryl 7 - [(2 - formamidothiazol - 4 - yl)glyoxylamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (6.0 g) with trifluoroacetic acid (23.7 g) in the presence of anisole (9.0 g) according to the similar manner to that of Example 9.

NMR δ ppm (DMSO-d_6): 3.75 (2H, q, J=17Hz), 5.27 (1H, d, J=5Hz), 5.37 (1H, d, J=11Hz), 5.63 (1H, d, J=17Hz), 5.83 (1H, dd, J=5Hz, 8Hz), 7.00 (1H, dd, J=11Hz, 17Hz), 8.50 (1H, s), 8.65 (1H, s), 9.93 (1H, d, J=8Hz), 12.8 (1H, broad s).

Preparation 47

7 - [(2 - Aminothiazol - 4 - yl)glyoxylamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (0.76 g) was obtained by reacting 7 - [(2 - formamidothiazol - 4 - yl)glyoxylamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (1.23 g) with conc. hydrochloric acid (1.25 ml) in a mixture of methanol (25 ml) and tetrahydrofuran (10 ml) according to the similar manner to that of Example 16.

I.R. (Nujol): 3300, 3200—3100, 1780, 1660, 1610, 1520 cm^{-1}.

NMR δ ppm (DMSO-d_6): 3.80 (2H, q, J=17Hz), 5.28.

Preparation 48

a) Sodium 7 - [2 - (2 - aminothiazol - 4 - yl)acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (1.36 g), which was prepared from 7 - [2 - (2 - aminothiazol - 4 - yl)acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (1.33 g) and sodium bicarbonate (0.304 g), was dissolved in N,N-dimethylformamide (14 ml). To this solution was added iodomethyl pivalate (0.932 g) in N,N - dimethylformamide (3 ml) under ice-cooling, followed by stirring at the same temperature for 10 minutes. After addition of ethyl acetate (80 ml), the reaction mixture was washed twice with water, three times with 5% aqueous solution of sodium bicarbonate and twice with an aqueous solution of sodium chloride in turn, dried over anhydrous magnesium sulfate, and then evaporated to dryness under reduced pressure to give a residue, which was pulverized with diisopropyl ether to obtain pivaloyloxymethyl 7 - [2 - (2 - aminothiazol - 4 - yl)-acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (1.0 g), mp 128—132°C (dec.).

I.R. (Nujol): 1770, 1750, 1650 cm^{-1}.

NMR δ ppm (DMSO-d_6): 1.18 (9H, s), 3.42 (2H, s), 3.80 (2H, q, J=17Hz), 5.18 (1H, d, J=5Hz), 5.40 (1H, d, J=11Hz), 5.68 (1H, d, J=17Hz), 5.77 (1H, dd, J=5Hz, 8Hz), 5.87 (2H, s), 6.30 (1H, s), 6.87 (2H, broad s), 6.88 (1H, dd, J=11Hz, 17Hz), 8.93 (1H, d, J=8Hz).

b) Privaloyloxymethyl 7 - [(2 - aminothiazol - 4 - yl)glyoxylamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (0.94 g) was obtained by reacting sodium 7 - [(2 - aminothiazol - 4 - yl)glyoxylamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (1.05 g) with iodomethyl pivalate (0.63 g) according to the similar manner to that of part a), mp 108—115°C.

I.R. (Nujol): 1775, 1745, 1660 cm^{-1}.

NMR δ ppm (DMSO-d_6): 1.12 (9H, s), 3.75 (2H, m), 5.22 (1H, d, J=5Hz), 5.38 (1H, d, J=11Hz), 5.67 (1H, d, J=18Hz), 5.78 (1H, dd, J=5Hz, 8Hz), 5.83 (2H, s), 6.85 (1H, dd, J=11Hz, 18Hz), 7.35 (2H, broad s), 7.83 (1H, s), 9.80 (1H, d, J=8Hz).

Preparation 49

To a solution of 7 - [(2 - aminothiazol - 4 - yl)glyoxylamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (1.0 g) in N,N - dimethylformamide (10 ml) were added triethylamine (0.27 g), 3-bromophthalide (0.56 g) and sodium iodide (0.39 g) at 10°C with stirring, and the stirring was continued at the same temperature for half an hour. After the reaction mixture was poured into water (50 ml), it was extracted with a mixture of tetrahydrofuran and ethyl acetate (1:1 by volume). The extract was washed with a saturated aqueous solution of sodium chloride and then dried over anhydrous magnesium sulfate, followed by evaporation to give an oil, which was pulverized with diisopropyl ether to obtain phthalid - 3 - yl 7 - [(2 - aminothiazol - 4 - yl)glyoxylamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (1.0 g).

I.R. (Nujol): 3300, 1770, 1650 cm^{-1}.

Preparation 50

7 - [(2 - Aminothiazol - 5 - yl)glyoxylamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (1.1 g) was obtained by reacting 7 - [(2 - formamidothiazol - 5 - yl)glyoxylamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (1.73 g) with conc. hydrochloric acid (2.2 g) according to a similar manner to that of Example 60, mp >250°C.

I.R. (Nujol): 3300, 3180, 1770, 1690, 1620, 1510, 1460 cm^{-1}.

NMR δ ppm (DMSO-d_6): 3.75 (2H, q, J=18Hz), 5.24 (1H, d, J=5Hz), 5.35 (1H, d, J=11Hz), 5.62 (1H, d, J=17Hz), 5.73 (1H, dd, J=5, 8Hz), 7.03 (1H, dd, J=11, 17Hz), 8.28 (1H, s), 8.56 (2H, broad s), 9.54 (1H, d, J=8Hz).

Preparation of the object compounds

Example 1

To a solution of benzhydryl 7 - amino - 3 - vinyl - 3 - cephem - 4 - carboxylate hydrochloride (1.9 g) and trimethylsilylacetamide (4.6 g) in ethyl acetate (30 ml) was added at −30°C a solution of the activated acid, which was prepared by stirring a mixture of 2 - (2 - formamidothiazol - 4 - yl) - 2 - methoxyimino-acetic acid (syn isomer) (1.1 g), phosphorus oxychloride (0.81 g), N,N-dimethylformamide (0.39 g) and ethyl acetate (20 ml) for half an hour under ice-cooling, and the mixture was stirred at −30 to −10°C for an hour. After addition of ethyl acetate (100 ml) and water (50 ml), the organic layer was separated out, washed with a saturated aqueous solution of sodium bicarbonate and an aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate and then evaporated to dryness to give benzhydryl 7 - [2 - (2 - formamidothiazol - 4 - yl) - 2 - methoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (2.4 g).

I.R. (Nujol): 3250, 1780, 1710, 1700, 1660, 1540 cm^{-1}.

NMR δ ppm (DMSO-d_6): 3.78 (2H, m), 3.95 (3H, s), 5.30 (1H, d, J=11Hz), 5.32 (1H, d, J=5Hz), 5.66 (1H, d, J=17Hz), 5.96 (1H, dd, J=5Hz, 8Hz), 6.82 (1H, dd, J=11Hz, 17Hz), 7.00 (1H, s) 7.17—7.73 (11H, m), 8.57 (1H, s), 9.80 (1H, d, J=8Hz), 12.7 (1H, broad s).

Example 2

Benzhydryl 7 - [2 - (2 - formamidothiazol - 4 - yl) - 2 - allyloxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (3.1 g) was obtained by reacting benzhydryl 7 - amino - 3 - vinyl - 3 - cephem - 4 - carboxylate hydrochloride (2.15 g) with 2 - (2 - formamidothiazol - 4 - yl) - 2 - allyloxy-iminoacetic acid (syn isomer) (1.53 g) according to the similar manner to that of Example 1.

I.R. (Nujol): 3250, 1760, 1710, 1690, 1660, 1530 cm^{-1}.

NMR δ ppm (DMSO-d_6): 3.75 (2H, q, J=18Hz), 4.65 (2H, d, J=5Hz), 5.00—6.3 (7H, m), 6.77 (1H, dd, J=11Hz, 18Hz), 6.97 (1H, s), 7.17—7.63 (11H, m), 8.53 (1H, s), 9.78 (1H, d, J=8Hz), 12.7 (1H, broad s).

Example 3

Benzhydryl 7 - [2 - (2 - formamidothiazol - 4 - yl) - 2 - propargyloxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (1.3 g) was obtained by reacting benzhydryl 7 - amino - 3 - vinyl - 3 - cephem - 4 - carboxylate hydrochloride (1.0 g) with 2 - (2 - formamidothiazol - 4 - yl) - 2 - propargyloxyiminoacetic acid (syn isomer) (0.71 g) according to the similar manner to that of Example 1.

I.R. (Nujol): 3250, 1780, 1720, 1690, 1660, 1550 cm^{-1}.

NMR δ ppm (DMSO-d_6): 3.38 (1H, m), 3.82 (2H, q, J=18Hz), 4.82 (2H, m), 5.33 (1H, d, J=5Hz), 5.35 (1H, d, J=11Hz), 5.55 (1H, d, J=18Hz), 5.98 (1H, dd, J=5Hz, 8Hz), 6.85 (1H, dd, J=11Hz, 18Hz), 7.02 (1H, s), 7.17—7.82 (10H, m), 7.55 (1H, s), 8.62 (1H, s), 9.80 (1H, d, J=8Hz), 12.60 (1H, broad s).

The compounds described in the following Examples 4 to 8 were obtained by reacting the 7 - amino - 3 - vinylcephalosporanic acid derivatives with the corresponding acid according to the similar manner to that of Example 1.

Example 4

7 - [2 - (2 - Aminothiazol - 4 - yl) - 2 - methoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid hydrochloride (syn isomer).

I.R. (Nujol): 3260, 1775, 1720, 1660, 1645, 1600, 1550 cm^{-1}.

Example 5

7 - [2 - (2 - Aminothiazol - 4 - yl) - 2 - allyloxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer).

I.R. (Nujol): 3250, 1770, 1655, 1605, 1545 cm^{-1}.

Example 6

7 - [2 - (2 - Aminothiazol - 4 - yl) - 2 - propargyloxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer).

I.R. (Nujol): 3250, 1760, 1680, 1620, 1530 cm^{-1}.

Example 7

Pivaloyloxymethyl 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - propargyloxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer).

I.R. (Nujol): 1770, 1740, 1670 cm^{-1}.

Example 8

Hexanoyloxymethyl 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - propargyloxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer).

I.R. (Nujol): 1770, 1650 cm^{-1}.

Example 9

To a suspension of benzhydryl 7 - [2 - (2 - formamidothiazol - 4 - yl) - 2 - methoxyiminoacetamido) - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (2.3 g) in methylene chloride (40 ml) were added anisole (3.3 g) and trifluoroacetic acid (8.7 g) under ice-cooling with stirring, and the stirring was continued at ambient temperature for 75 minutes. After evaporation of the reaction mixture, to the residue were added water and ethyl acetate, followed by adjusting to pH 7 with a saturated aqueous solution of sodium bicarbonate. To the separated aqueous solution was added ethyl acetate, followed by adjusting to pH 2 with 10% hydrochloric acid. The ethyl acetate layer was separated out, washed with an aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate and then evaporated to dryness to give a residue, which was washed with diethyl ether to obtain 7 - [2 - (2 - formamidothiazol - 4 - yl) - 2 - methoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer) (1.45 g).

I.R. (Nujol): 3250, 1770, 1690, 1650, 1540 cm^{-1}.

NMR δ ppm (DMSO-d_6): 3.70 (2H, q, J=17Hz), 3.88 (3H, s), 5.20 (1H, d, J=5Hz), 5.30 (1H, d, J=11Hz), 5.55 (1H, d, J=18Hz), 5.82 (1H, dd, J=5Hz, 8Hz), 6.93 (1H, dd, J=11Hz, 18Hz), 7.45 (1H, s), 8.52 (1H, s), 9.73 (1H, d, J=8Hz).

Example 10

7 - [2 - (2 - Formamidothiazol - 4 - yl) - 2 - allyloxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer) (1.7 g) was obtained by reacting benzhydryl 7 - [2 - (2 - formamidothiazol - 4 - yl) - 2 - allyloxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (3.0 g) with trifluoroacetic acid (10.8 g) in the presence of anisole (4.0 g) according to the similar manner to that of Example 9.

I.R. (Nujol): 3250, 1770, 1680 (shoulder), 1650, 1530 cm^{-1}.

NMR δ ppm (DMSO-d_6): 3.67 (2H, q, J=18Hz), 4.60 (2H, d, J=4Hz), 4.83—6.33 (7H, m), 6.90 (1H, dd, J=11Hz, 18Hz), 7.38 (1H, s), 8.48 (1H, s), 9.70 (1H, d, J=8Hz), 12.62 (1H, broad s).

Example 11

7 - [2 - (2 - Formamidothiazol - 4 - yl) - 2 - propargyloxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer) (0.77 g) was obtained by reacting benzhydryl 7 - [2 - (2 - formamidothiazol - 4 - yl) - 2 - propargyloxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (1.2 g) with trifluoroacetic acid (4.4 g) in the presence of anisole (1.7 g) according to the similar manner to that of Example 9.

I.R. (Nujol): 3250, 1780, 1680, 1660, 1550 cm^{-1}.

NMR δ ppm (DMSO-d_6): 3.52 (1H, m), 3.77 (2H, q, J=18Hz), 4.80 (2H, m), 5.27 (1H, d, J=5Hz, 5.37 (1H, d, J=11Hz), 5.62 (1H, d, J=18Hz), 5.87 (1H, dd, J=5Hz, 8Hz), 7.00 (1H, dd, J=11Hz, 18Hz), 7.50 (1H, s), 8.57 (1H, s), 9.83 (1H, d, J=8Hz), 12.77 (1H, broad s).

The compounds described in the following Examples 12 to 14 were obtained by reacting benzhydryl ester of the corresponding cephalsporanic acid derivatives with trifluoroacetic acid in the presence of anisole according to the similar manner to that of Example 9.

Example 12

7 - [2 - (2 - Aminothiazol - 4 - yl) - 2 - methoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid hydrochloride (syn isomer).

I.R. (Nujol): 3260, 1775, 1720, 1660, 1645, 1600, 1550 cm^{-1}.

Example 13

7 - [2 - (2 - Aminothiazol - 4 - yl) - 2 - allyloxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer).

I.R. (Nujol): 3250, 1770, 1655, 1605, 1545 cm^{-1}.

Example 14

7 - [2 - (2 - Aminothiazol - 4 - yl) - 2 - propargyloxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer).

I.R. (Nujol): 3250, 1760, 1680, 1620, 1530 cm^{-1}.

Example 15

To a solution of 7 - [2 - (2 - formamidothiazol - 4 - yl) - 2 - methoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer) (1.4 g) in methanol (30 ml) and tetrahydrofuran (20 ml) was added conc. hydrochloric acid (1.0 ml), and the mixture was stirred at ambient temperature for 2.7 hours. After evaporation of the reaction mixture, the residue was washed with tetrahydrofuran to give 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - methoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid hydrochloride (syn isomer) (1.2 g).

I.R. (Nujol): 3260, 1775, 1720, 1660, 1645, 1600, 1550 cm^{-1}.

NMR δ ppm ($DMSO-d_6$): 3.75 (2H, q, J=18Hz), 4.00 (3H, s), 5.25 (1H, d, J=5Hz), 5.35 (1H, d, J=11Hz), 5.60 (1H, d, J=18Hz), 5.80 (1H, dd, J=5Hz, 8Hz), 6.98 (1H, dd, J=11Hz, 18Hz), 7.02 (1H, s), 9.87 (1H, d, J=8Hz).

Example 16

A mixture of 7 - [2 - (2 - formamidothiazol - 4 - yl) - 2 - allyloxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer) (1.6 g) and conc. hydrochloric acid (1.5 ml) in methanol (30 ml) was stirred at ambient temperature for 2 hours. After evaporation of the reaction mixture, thereto was added a saturated aqueous solution of sodium bicarbonate, followed by removing the insoluble substance of filtration. The filtrate was adjusted to pH 3 with 10% hydrochloric acid, and the precipitated solid was collected by filtration and washed with water to give 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - allyloxyimino-acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer) (1.25 g).

I.R. (Nujol): 3250, 1770, 1655, 1605, 1545 cm^{-1}.

NMR δ ppm ($DMSO-d_6$): 3.75 (2H, q, J=18Hz), 4.67 (2H, m), 5.00—6.5 (1H, m), 6.80 (1H, s), 7.00 (1H, dd, J=11Hz, 18Hz), 9.67 (1H, d, J=8Hz).

Example 17

7 - [2 - (2 - Aminothiazol - 4 - yl) - 2 - propargyloxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer) (0.5 g) was obtained by reacting 7 - [2 - (2 - formamidothiazol - 4 - yl) - 2 - propargyloxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer) with conc. hydrochloric acid (0.5 ml) in a mixture of methanol (14 ml) and tetrahydrofuran (4 ml) according to the similar manner to that of Example 16.

I.R. (Nujol): 3250, 1760, 1680, 1620, 1530 cm^{-1}.

NMR δ ppm ($DMSO-d_6$): 3.43 (1H, m), 3.68 (2H, q, J=18Hz), 4.7 (2H, m), 5.17 (1H, d, J=4Hz), 5.28 (1H, d, J=12Hz), 5.53 (1H, d, J=18Hz), 5.73 (1H, dd, J=4Hz, 8Hz), 6.83 (1H, s), 6.92 (1H, dd, J=12Hz, 18Hz), 9.67 (1H, d, J=8Hz).

The compounds described in the following Examples 18 and 19 were obtained by reacting the corresponding cephalosporanic acid derivatives having formamido group with conc. hydrochloric acid according to the similar manner to that of Example 16.

Example 18

Pivaloyloxymethyl 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - propargyloxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer).

I.R. (Nujol): 1770, 1740, 1670 cm^{-1}.

Example 19

Hexanoyloxymethyl 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - propargyloxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer).

I.R. (Nujol): 1770, 1650 cm^{-1}.

Example 20

Privaloyloxymethyl 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - propargyloxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (1.64 g) was obtained by reacting sodium 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - propargyloxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (2 g) with iodomethyl pivalate (1.21 g) according to the similar manner to that of Preparation 48a, mp 163—185°C (dec.).

I.R. (Nujol): 1770, 1740, 1670 cm^{-1}.

NMR δ ppm ($DMSO-d_6$): 1.22 (9H, s), 3.5 (1H, s), 3.85 (2H, q, J=18Hz), 4.75 (1H, s), 5.35 (1H, d, J=5Hz), 5.45 (1H, d, J=11Hz), 5.70 (1H, d, J=18Hz), 5.85 (1H, dd, J=5Hz, 8Hz), 5.92 (2H, s), 6.87 (1H, s), 6.88 (1H, dd, J=11Hz, 18Hz), 7.32 (2H, m), 9.73 (1H, d, J=8Hz).

Example 21

To a solution of sodium 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - propargyloxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (2 g) in N,N-dimethylformamide (20 ml) was added a solution of iodomethyl hexanoate (1.28 g) in N,N-dimethylformamide (4 ml) under ice-cooling, and the mixture was stirred at the same temperature for 15 minutes. To the reaction mixture was added ethyl acetate (80 ml), followed by washing twice with water, three times with 5% aqueous solution of sodium bicarbonate and twice with a saturated aqueous solution of sodium chloride. The resultant solution was dried over anhydrous magnesium sulfate and then evaporated to give a residue, which was pulverized with diisopropyl ether to obtain hexanoyloxymethyl 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - propargyloxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (1.85 g), mp 98—109°C (dec.).

I.R. (Nujol): 1770, 1650 cm^{-1}.

NMR δ ppm (DMSO-d_6): 0.87 (3H, t, J=8Hz), 1.38 (6H, m), 2.53 (2H, m), 3.47 (1H, s), 3.80 (2H, q, J=18Hz), 4.72 (2H, s), 5.27 (1H, d, J=5Hz), 5.42 (1H, d, J=11Hz), 5.70 (1H, d, J=18Hz), 5.88 (3H, m), 6.80 (1H, s), 6.80 (1H, dd, J=11Hz, 18Hz), 7.25 (2H, broad s), 9.70 (1H, d, J=8Hz).

Example 22

The activated acid, which was prepared from 2-tert-butoxycarbonylmethoxyimino-2-(2-formamidothiazol-4-yl)-acetic acid (syn isomer) 13.8g), N,N-dimethylformamide (3.66 g) and phosphorus oxychoride (7.7 g) in tetrahydrofuran (80 ml) in a conventional manner, was added to a solution of benzhydryl 7-amino-3-vinyl-3-cephem-4-carboxylate hydrochloride (15 g) and trimethylsilylacetamide (32 g) in ethyl acetate (150 ml) at −20°C with stirring, and the stirring was continued at the same temperature for half an hour. After addition of water (100 ml), the ethyl acetate layer was separated out, and washed with an aqueous solution of sodium chloride, an aqueous solution of sodium bicarbonate and then an aqueous solution of sodium chloride in turn, followed by drying, over anhydrous magnesium sulfate. Removal of the solvent gave an oil, which was pulverized with diisopropyl ether and washed with the same to obtain benzhydryl 7-[2-tert-butoxycarbonylmethoxyimino-2-(2-formamidothiazol-4-yl)acetamido]-3-vinyl-3-cephem-4-carboxylate (syn isomer) (23.1 g), mp 101°C (dec.).

I.R. (Nujol): 3250, 1780, 1720, 1680, 1540 cm^{-1}.

N.M.R. δ ppm (DMSO-d_6): 1.45 (9H, s), 3.77 (2H, q, J=18Hz), 4.64 (2H, s), 5.32 (1H, d, J=5Hz), 5.2—6.0 (2H, m), 5.97 (1H, dd, J=5Hz, 8Hz), 6.5—7.6 (1H, m), 6.98 (1H, s), 7.2—7.8 (11H, m), 8.55 (1H, s), 9.68 (1H, d, J=8Hz), 12.71 (1H, broad s).

The following compounds were obtained by reacting 7-amino-3-vinyl cephalosporanic acid derivatives with the ocrresponding acids according to the similar manner to that of Example 22.

Example 23

Pivaloyloxymethyl 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - methoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer).

I.R. (Nujol): 3400—3100, 1770, 1745, 1670, 1610, 1530 cm^{-1}.

Example 24

Phthalid - 3 - yl 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - methoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer).

I.R. (Nujol): 3300, 1775, 1670, 1610, 1530 cm^{-1}.

Example 25

Benzhydryl 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - tert - butoxy - carbonylmethoxyimino-acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer).

I.R. (Nujol): 3440, 3260, 3100, 1780, 1720, 1660, 1530 cm^{-1}.

Example 26

A mixture of benzhydryl 7 - [2 - tert - butoxycarbonylmethoxyimino - 2 - (2 - formamidothiazol - 4 - yl)acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (19.0 g) and conc. hydrochloric acid (11.6 g) in methanol (380 ml) was stirred at ambient temperature for 15 minutes. After addition of water (200 ml), the reaction mixture was neutralized with sodium bicarbonate, followed by removing the methanol under reduced pressure. The resultant aqueous solution was extracted three times with ethyl acetate, and the combined extract was washed with water and an aqueous solution of sodium chloride, and then dried over anhydrous magnesium sulfate. Removal of the solvent gave an oil, which was pulverized with diisopropyl ether to obtain benzhydryl 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - tert - butoxycarbonyl-methoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (15.3 g).

I.R. (Nujol): 3440, 3260, 3100, 1780, 1720, 1660, 1530 cm^{-1}.

N.M.R. δ ppm (DMSO-d_6): 1.44 (9H, s), 3.77 (2H, q, J=18Hz), 4.58 (2H, s), 5.29 (1H, d, J=5Hz), 5.1—5.9 (2H, m), 5.90 (1H, dd, J=5Hz, 8Hz), 6.5—7.8 (13H, m), 6.83 (1H, s), 6.93 (1H, s), 9.56 (1H, d, J=8Hz).

The following compounds were obtained by reacting 7-acylamino-3-vinyl cephalosporanic acid derivatives having a formamido group with hydrochloric acid acording to the similar manner to that of Example 26.

Example 27

Pivaloyloxymethyl 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - methoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer).

I.R. (Nujol): 3400—3100, 1770, 1745, 1670, 1610, 1530 cm^{-1}.

Example 28

Phthalid - 3 - yl 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - methoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer).

I.R. (Nujol): 3300, 1775, 1670, 1610, 1530 cm^{-1}.

Example 29

7 - [2 - (2 - Aminothiazol - 4 - yl) - 2 - carboxymethoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer).

I.R. (Nujol): 3350, 1770, 1680, 1640 cm^{-1}.

Example 30

Sodium 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - methoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (2.9 g), which was prepared from 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - methoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid and sodium bicarbonate in a conventional manner was dissolved in N,N-dimethylformamide (30 ml), and thereto was added dropwise a solution of iodomethyl pivalate (1.62 g) in N,N-dimethylformamide (5 ml) under ice-cooling with stirring, and the stirring was continued at the same temperature for 10 minutes. To the reaction mixture were added ethyl acetate (200 ml) and water (150 ml), followed by separating out the organic layer, which was washed with a saturated aqueous solution of sodium bicarbonate and an aqueous solution of sodium chloride, and then dried over anhydrous magnesium sulfate. Removal of the solvent gave an oil, which was pulverized with diisopropyl ether to obtain pivaloyloxymethyl 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - methoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (2.1 g).

I.R. (Nujol): 3400—3100, 1770, 1745, 1670, 1610, 1530 cm^{-1}.

N.M.R. δ ppm (DMSO-d_6): 1.18 (9H, s), 3.77 (2H, q, J=18Hz), 3.84 (3H, s), 5.23 (1H, d, J=5Hz), 5.38 (1H, d, J=11Hz), 5.69 (1H, d, J=18Hz), 5.64—6.00 (3H, m), 6.75 (1H, s), 6.82 (1H, dd, J=11Hz, 18Hz), 7.24 (2H, broad s), 9.60 (1H, d, J=8Hz).

Example 31

To a solution of sodium 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - methoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (2.16 g) in N,N-dimethylformamide (20 ml) were added 3-bromophthalide (1.3 g) and sodium iodide (1.35 g), and the mixture was stirred at ambient temperture for 40 minutes. Thereto were added ethyl acetate (100 ml) and water (50 ml), and the separated ethyl acetate layer was washed with a saturated aqueous solution of sodium bicarbonate and an aqueous solution of sodium chloride, and then dried over anhydrous magnesium sulfate. After removal of the solvent, the residue (2.6 g) was chromatographed on silica gel (50 g) using a mixture of benzene and ethyl acetate as an eluent. The fractions containing the desired compound were collected and evaporated to give phthalid - 3 - yl 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - methoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (1.4 g).

I.R. (Nujol): 3300, 1775, 1670, 1610, 1530 cm^{-1}.

N.M.R. δ ppm (DMSO-d_6): 3.80 (2H, m), 3.88 (3H, s), 5.23 (1H, d, J=4Hz), 5.20—6.00 (3H, m), 6.78 (s) / 6.82 (s) } 1H), 7.05 (1H, dd, J=11Hz, 17Hz), 7.65 (s) / 7.68 (s) } 1H), 7.67—8.10 (4H, m), 9.67 (d, J=8Hz) / 9.70 (d, J=8Hz) } (1H)

Example 32

To a suspension of benzhydryl 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - tert - butoxycarbonylmethoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (15.0 g) in anisole (15 ml) was added 2,2,2-trifluoroacetic acid (60 ml) under ice-cooling with stirring, and the stirring was continued at 10 to 15°C for 80 minutes. After the reaction mixture was poured into diisopropyl ether (600 ml), the insoluble substance was collected by filtration and then dried. This substance (11.2 g) was dissolved in an aqueous solution of sodium bicarbonate so as to adjust the resultant solution to pH 6.0, and then chromatographed on alumina (44.8 ml) using 5% aqueous sodium acetate as an eluent. The fractions containing the desired compound were collected and evaported to dryness to give 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - carboxymethoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer) (3.55 g), mp>250°C.

I.R. (Nujol): 3350, 1770, 1680, 1640 cm^{-1}.

N.M.R. δ ppm (DMSO-d_6): 3.70 (2H, q, J=18Hz), 4.62 (2H, s), 5.21 (1H, d, J=5Hz), 5.82 (1H, dd, J=5Hz, 8Hz), 5—6 (2H, m), 6.82 (1H, s), 7.22 (2H, broad s), 6.5—7.5 (1H, m), 9.50 (1H, d, J—8Hz).

Example 33

A mixture of benzhydryl 7 - [2 - (2 - formamidothiazol - 4 - yl) - 2 - methoxyiminoacetamido] - 3 - triphenylphosphoranylidenemethyl - 3 - cephem - 4 - carboxylate (syn isomer) (2.2 g), 36% aqueous formaldehyde (20 ml) and tetrahydrofuran (60 ml) were stirred at ambient temperature for 12.5 hours. After addition of ethyl acetate (100 ml) to the reaction mixture, the organic layer was separated out, washed with 10% hydrochloric acid and an aqueous solution of sodium chloride, and then dried over anhydrous magnesium sulfate. Removal of the solvent gave a residue, which was pulverized with diethyl ether, and chromatographed on silica gel using chloroform and then a mixture of chloroform and acetone (19:1 and 9:1 by volume) as an eluent. The fractions containing the desired compound were collected and evaporated to give benzhydryl 7 - [2 - (2 - formamidothiazol - 4 - yl) - 2 - methoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (0.25 g).

I.R. (Nujol): 3250, 1780, 1710, 1700, 1660, 1540 cm^{-1}.

Example 34

[4 - Benzhydryloxycarbonyl - 7 - {2 - tert - butoxycarbonylmethoxyimino - 2 - (formamidothiazol - 4 - yl)acetamido} - 3 - cephem - 3 - yl]methyltriphenyl - phosphonium iodide (syn isomer) (0.59 g) was dissolved in a mixture of methylene chloride (20 ml), water (10 ml) and 36% aqueous formaldehyde (1 ml), followed by adjusting to pH 8.0 with 20% aqueous sodium carbonate. After stirring for 3 hours at 30—35°C, the reaction mixture was further adjusted to pH 2.0 with 10% hydrochloric acid and then extracted with methylene chloride. The extract was washed with an aqueous sodium chloride dried over magnesium sulfate and then evaporated. The residue (0.46 g) was chromatogrphed on silica gel using a mixed solvent of benzene and ethyl acetate (2:1 by volume) as an eluent to obtain benzhydryl 7 - [2 - tert - butoxycarbonylmethoxyimino - 2 - (2 - formamidothiazol - 4 - yl)acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (0.14 g).

I.R. (Nujol): 3250, 1780, 1720, 1680, 1540 cm^{-1}.

The following compounds were obtained by reacting 7 - acylamino - 3 - triphenylphosphoranylidene-methylcephalosporanic acid derivative with an aqueous formaldehyde according to the similar manner to that of Examples 33 and 34.

Example 35

Pivaloyloxymethyl 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - methoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer).

I.R. (Nujol): 3400—3100, 1770, 1745, 1670, 1610, 1530 cm^{-1}.

Example 36

Phthalid - 3 - yl 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - methoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer).

I.R. (Nujol): 3300, 1775, 1670, 1610, 1530 cm^{-1}.

Example 37

To a solution of benzhydryl 7 - amino - 3 - vinyl - 3 - cephem - 4 - carboxylate (3.02 g) in methylene chloride (30 ml) were added a solution of 2 - (2 - formamidothiazol - 4 - yl) - 2 - (L - 2 - benzhydryloxycarbonyl - 2 - tert - butoxycarbonylaminoethoxycarbonylmethoxyimino)acetic acid (syn isomer) (5.5 g) and then N,N'-dicycylohexylcarbodiimide (1.81 g), followed by stirring at ambient temperature for 2 hours. Diethyl ether (100 ml) was added to the reaction mixture, and the precipitated material was removed by filtration. After removing the solvent from the filtrate, the residue was dissolved in ethyl acetate, washed with 5% aqueous sodium bicarbonate and then an aqueous sodium chloride, followed by drying over anhydrous magnesium sulfate. Removal of the solvent gave a residue (10 g), which was chromatographed on silica gel (200 ml) eluting with a mixed solvent of diisopropyl ether and acetone. Fractions containing a desired compound were collected and evaporated to obtain benzhydryl 7 - [2 - (2 - formamidothiazol - 4 - yl) - 2 - (L - 2 - benzhydryloxycarbonyl - 2 - tert - butoxycarbonyl-aminoethoxycarbonylmethoxyimino)acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (5.9 g). mp 87—94°C.

I.R. (Nujol): 3350, 1780, 1720, 1700, (broad) cm^{-1}.

N.M.R. δ ppm (DSMO-d_6): 1.33 (9H, s), 3.57, 3.96 (2H, ABq, J=18Hz), 4.53 (3H, m), 4.73 (2H, broad s), 5.3 (1H, d, J=11Hz), 5.33 (1H, d, J=5Hz), 5.53 (1H, d, J=18Hz), 6.00 (1H, dd, J=5Hz, 8Hz), 6.87 (1H, s), 7.00 (1H, s), 7.4 (20H, m), 7.50 (1H, s), 8.57 (1H, s) 9.80 (1H, d, J=8Hz), 12.7 (1H, broad s).

Example 38

To a solution of benzhydryl 7 - amino - 3 - vinyl - 3 - cephem - 4 - carboxylate (3.54 g) in methylene chloride (35 ml) were added a solution of 2 - (2 - formamidothiazol) - 4 - yl) - 2 - (DL - 3 - benzhydryloxy-carbonyl - 3 - tert - butoxycarbonylaminopropoxyimino)acetic acid (syn isomer) (6.0 g) in tetrahydrofuran (60 ml) and then N,N'-dicyclohexylcarbodiimide (2.2 g), followed by stirring at ambient temperature for 4 hours. The precipitated material was removed by filtration, and the filtrate was evaporated to dryness to give a residue, which was chromatographed on silica gel eluting with a mixed solvent of diisopropyl ether

and acetone. Fractions containing a desired compound were collected and evaporated to obtain benzhydryl 7 - [2 - (2 - formamidothiazol - 4 - yl) - 2 - (DL - 3 - benzhydryloxycarbonyl - 3 - tert - butoxycarbonyl-aminopropoxyimino)acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (3.80 g), mp 153—158°C.

I.R. (Nujol): 3200, 1780, 1700 (broad) cm^{-1}.

N.M.R. δ ppm ($DMSO-_6$): 1.36 (9H, s), 2.1 (2H, m), 3.6 (2H, m), 4.2 (3H, m), 5.2—6.1 (4H, m), 6.8 (1H, s), 6.97 (1H, s), 6.8—7.2 (1H, m), 7.37 (20H, m), 7.43 (1H, s), 8.53 (1H, s), 9.75 (1H, d, J=8Hz), 12.7 (1H, broad s).

Example 39

To a solution of N,N-dimethylformamide (1.10 ml) and tetrahydrofuran (6 ml) was added dropwise phosphorus oxychloride (1.30 ml), followed by stirring for 10 minutes. After addition of tetrahydrofuran (25 ml) and 2 - (2 - formamidothiazol - 4 - yl) - 2 - methoxyiminoacetic acid (syn isomer) (2.96 g), the mixture was stirred at 5°C for 45 minutes to prepare the activated acid solution. This solution was added dropwise to a solution of L - 2 - benzhydryloxycarbonyl - 2 - tert - butoxy - carbonylaminoethyl 7 - amino - 3 - vinyl - 3 - cephem - 4 - carboxylate (5.0 g) and trimethylsilylacetamide (9.05 g) in methylene chloride (50 ml) at −30°C in the course of 5 minutes, followed by stirring at −20 to −10°C for half an hour. The reaction mixture was poured into a mixture of ethyl acetate (300 ml) and water (100 ml), and then adjusted to pH 7.5 with 10% aqueous sodium hydroxide and an aqueous sodium bicarbonate. The separated ethyl acetate solution was washed with an aqueous sodium chloride and then dried over anhydrous magnesium sulfate. Removal of the solvent gave crude product (7.5 g) of L - 2 - benzhydryloxycarbonyl - 2 - tert - butoxy-carbonylaminoethyl 7 - [2 - (2 - formamidothiazol - 4 - yl) - 2 - methoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer).

I.R. (Nujol): 3280, 1782, 1709, 1689, 1656 cm^{-1}.

N.M.R. δ ppm ($DMSO-d_6$): 1.40 (9H, s), 3.73 (2H, m), 3.92 (3H, s), 4.56 (3H, m), 5.20 (1H, d, J=5Hz), 5.33 (1H, d, J=11Hz), 5,65 (1H, d, J=18Hz), 5.75 (1H, dd, J=5Hz, 8Hz), 6.84 (1H, s), 6.93 (1H, dd, J=11Hz, 18Hz), 7.37 (10H, m), 7.43 (1H, s), 8.53 (1H, s), 9.73 (1H, d, J=8Hz, 12.7 (1H, broad s).

Example 40

Benzhydryl 7 - [2 - 2 - formamidothiazol - 5 - yl) - 2 - methoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (2.9 g), mp 208°C (dec.), was obtained by reacting benzhydryl 7 - amino - 3 - cephem - 4 - carboxylate hydrochloride (2.28 g) with 2 - (2 - formamidothiazol - 5 - yl) - 2 - methoxyiminoacetic acid (syn isomer) (1.4 g) according to a similar manner to those of Example 39.

I.R. (Nujol): 3250, 1780, 1720, 1685, 1655, 1570 cm^{-1}.

N.M.R. δ ppm ($DMSO-d_6$): 3.82 (2H, q, J=18Hz), 3.92 (3H, s), 5.30 (1H, d, J=11Hz), 5.32 (1H, d, J=5Hz), 5.67 (1H, d, J=17Hz), 5.92 (1H, dd, J=5.8Hz), 6.85 (1H, dd, J=11Hz, 17Hz), 7.00 (1H, s), 7.2—7.6 (10H, m), 7.61 (1H, s), 8.62 (1H, s), 9.98 (1H, d, J=8Hz).

Example 41

Benzhydryl 7 - [2 - (2 - formamidothiazol - 5 - yl) - 2 - methoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (anti isomer) (4.14 g) was obtained by reacting benzhydryl 7 - amino - 3 - vinyl - 3 - cephem - 4 - carboxylate hydrochloride (3.26 g) with 2 - (2 - formamidothiazol - 5 - yl) - 2 - methoxyiminoacetic acid (anti isomer) (2.0 g) according to a similar manner to those of Example 39.

I.R. (Nujol): 3250, 1780, 1720, 1685, 1660 cm^{-1}.

N.M.R. δ ppm ($DMSO-d_6$): 3.79 (2H, q, J=18Hz), 4.12 (3H, s), 5.34 (1H, d, J=5Hz), 5.31 (1H, d, J=11Hz), 5.65 (1H, d, J=18Hz), 5.83 (1H, dd, J=5Hz, 8Hz), 6.83 (1H, dd, J=11Hz, 18Hz), 7.00 (1H, s), 7.42 (10H, broad s), 8.62 (1H, s), 9.55 (1H, d, J=8Hz).

Example 42

Benzhydryl 7 - [2 - (2 - formamidothiazol - 4 - yl) - 2 - ethoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (25.0 g) was obtained by reacting benzhydryl 7 - amino - 3 - vinyl - 3 - cephem - 4 - carboxylate hydrochloride (17.2 g) with 2 - (2 - formamidothiazol - 4 - yl) - 2 - ethoxyiminoacetic acid (syn isomer) (8.8 g) according to a similar manner to those of Exampe 39.

I.R. (Nujol): 3260, 3150, 1770, 1720, 1700, 1660, 1620, 1560, 1540 cm^{-1}.

N.M.R. δ ppm ($DMSO-d_6$): 1.27 (3H, t, J=7Hz), 3.79 (2H, q, J=17Hz), 4.18 (2H, q, J=7Hz), 5.32 (1H, d, J=5Hz), 5.33 (1H, d, J=11Hz), 5.65 (1H, d, J=17Hz), 5.96 (1H, dd, J=5Hz, 8Hz), 6.78 (1H, dd, J=11Hz, 17Hz), 6.97 (1H, s), 7.17—7.67 (11H, m), 8.55 (1H, s), 9.73 (1H, d, J=8Hz), 12.70 (1H, broad s).

Example 43

Benzhydryl 7 - [2 - (2 - formamidothiazol - 4 - yl) - 2 - hexyloxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (5.7 g) was obtained by reacting benzhydryl 7 - amimo - 3 - vinyl - 3 - cephem - 4 - carboxylate hydrochloride (4.29 g) with 2 - (2 - formamidothiazol - 4 - yl) - 2 - hexyloxyiminoacetic acid (syn isomer) (3.29 g) according to a similar manner to those of Example 39.

I.R. (Nujol): 3250, 1770, 1710, 1700, 1650, 1570, 1535 cm^{-1}.

N.M.R. δ ppm ($DMSO-d_6$): 0.87 (3H, t, J=6Hz), 1.0—2.0 (8H, m), 3.75 (2H, ABq, J=18Hz), 4.12 (2H, t, J=6Hz), 5.28 (1H, d, J=5Hz), 5.42 (1H, d, J=11Hz), 5.62 (1H, d, J=17Hz), 5.90 (1H, dd, J=5Hz, 8Hz), 6.77 (1H,

dd, J=11Hz, 17Hz), 6.97 (1H, s), 7.12—7.75 (11H, m), 8.50 (1H, s), 9.52 (1H, d, J=8Hz), 12.70 (1H, broad s).

The following compounds were obtained by reacting 7-amino-3-vinyl cephalosporanic acid derivatives with hydrochloride of the corresponding acid according to a similar manner to those of Example 39.

Example 44

7 - [2 - (2 - Aminothiazol - 5 - yl) - 2 - methoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer), mp>250°C.

I.R. (Nujol): 3300, 1780, 1645, 1580, 1515 cm^{-1}.

Example 45

7 - [2 - (2 - Aminothiazol - 5 - yl) - 2 - methoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (anti isomer), mp>250°C.

I.R. (Nujol): 3320, 1775, 1655, 1575, 1515 cm^{-1}.

Example 46

7 - [2 - (2 - Aminothiazol - 4 - yl) - 2 - ethoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer).

I.R. (Nujol): 3300, 1770, 1660, 1545 cm^{-1}.

Example 47

Pivaloyloxymethyl 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - pivaloyloxymethoxycarbonylmethoxyimino)acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer), mp 115°C (dec.).

I.R. (Nujol): 3400, 3260, 3100, 1780, 1750, 1660, 1530 cm^{-1}.

Example 48

Pivaloyloxymethyl 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - ethoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer).

I.R. (Nujol): 3300, 1780, 1740, 1670, 1610, 1530 cm^{-1}.

Example 49

7 - [2 - (2 - Aminothiazol - 4 - yl) - 2 - hexyloxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer), mp 147—155°C (dec.).

I.R. (Nujol): 3250, 1770, 1660, 1530 cm^{-1}.

Example 50

Acetoxymethyl 7 - [2 - (2 - amimothiazol - 4 - yl) - 2 - methoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer), mp 78—83°C.

I.R. (Nujol): 3300, 1765 (broad), 1660, 1610, 1535 cm^{-1}.

Example 51

Propionyloxymethyl 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - methoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer), mp 79—85°C.

I.R. (Nujol): 3350, 1770 (broad), 1650, 1620, 1530 cm^{-1}.

Example 52

Isobutyryloxymethyl 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - methoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer), mp 92—100°C (dec.).

I.R. (Nujol): 3400—3100, 1780—1740, 1670, 1610, 1530 cm^{-1}.

Example 53

1 - Acetoxypropyl 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - methoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer), mp 97—101°C.

I.R. (Nujol): 3300, 1765, 1670, 1610 cm^{-1}.

Example 54

L - 2 - Amino - 2 - carboxyethyl 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - methoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer).

I.R. (Nujol): 3200, 1770, 1735 (shoulder), 1650 (broad) cm^{-1}.

Example 55

Benzhydryl 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - (L - 2 - benzhydryloxycarbonyl - 2 - tert - butoxycarbonylaminoethoxycarbonylmethoxyimino)acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer), mp 124—128°C.

IR (Nujol): 3360, 1750 (broad) cm^{-1}.

Example 56

Benzhydryl 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - (DL - 3 - benzhydryloxycarbonyl - 3 - tert - butoxycarbonylaminopropoxyimino)acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer), mp 119—122°C.

I.R. (Nujol): 3300, 1780, 1719, 1680 cm^{-1}.

Example 57

To a solution of benzhydryl 7 - [2 - (2 - formamidothiazol - 4 - yl) - 2 - (L - 2 - benzhydryloxycarbonyl - 2 - tert - butoxycarbonylaminoethoxycarbonylmethoxyimino)acetamido) - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer] (6.9 g) in methanol (140 ml) was added conc. hydrochloric acid (3.1 ml), and the mixture was stirred at 35°C for 90 minutes. The reaction mixture was adjusted to pH 6.0 with 5% aqueous sodium bicarbonate and then diluted with water (200 ml). Removal of the methanol gave an aqueous solution, which was extracted with ethyl acetate. The extract was washed with an aqueous sodium chloride and then dried over anhydrous magnesium sulfate, followed by removal of the solvent. The residue was pulverized with diisopropyl ether and collected by filtration to obtain benzhydryl 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - (L - 2 - benzhydryloxycrbonyl - 2 - tert - butoxycarbonylaminoethoxycarbonylmethoxyimino) - acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (5.5 g), mp 124—128°C.

I.R. (Nujol): 3360, 1750 (broad) cm^{-1}.

N.M.R. δ ppm (DMSO-d_6): 1.40 (9H, s), 3.57, 3.98 (2H, ABq, J=18Hz), 4.50 (3H, m), 4.63 (2H, broad s), 5.30 (1H, d, J=11Hz), 5.31 (1H, d, J=5Hz), 5.67 (1H, d, J=18Hz), 5.95 (1H, dd, J=5Hz, 8Hz), 6.86 (2H, s), 6.8—7.20 (1H, m), 7.00 (1H, s), 7.40 (10H, s), 9.65 (1H, d, J=8Hz).

Example 58

To a solution of benzhydryl 7 - [2 - (2 - formamidothiazol - 4 - yl) - 2 - (DL - 3 - benzhydryloxycarbonyl - 3 - tert - butoxycarbonylaminopropoxyimino)acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (3.65 g) in methanol (190 ml) was added conc. hydrochloric acid (1.96 ml), and the mixture was stirred at 35°C for 24 minutes. The reaction mixture was adjusted to pH 6.5 with 10% aqueous sodium hydroxide and 5% aqueous sodium bicarbonate, followed by removal of the methanol. The residue was dissolved in ethyl acetate, washed with an aqueous sodium chloride and then dried over anhydrous magnesium sulfate. Removal of the solvent gave a residue, which was pulverized with diisopropyl ether to obtain benzhydryl 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - (DL - 3 - benzhydryloxycarbonyl - 3 - tert - butoxycarbonylaminopropoxyimino)acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (3.5 g), mp 119—122°C.

I.R. (Nujol): 3300, 1780, 1719, 1680 cm^{-1}.

N.M.R. δ ppm (DMSO-d_6): 1.37 (9H, s), 2.1 (2H, m), 3.7 (2H, m), 4.2 (3H, m), 5.2—6.1 (4H, m), 6.8 (2H, s), 6.8—7.2 (1H, m), 6.97 (1H, s), 7.37 (20H, s), 9.67 (1H, d, J=8Hz).

Example 59

To a solution of L - 2 - benzhydryloxycarbonyl - 2 - tert - butoxycarbonylaminoethyl 7 - [2 - (2 - formamidothiazol - 4 - yl) - 2 - methoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (6.8 g) in methanol (300 ml) was added conc. hydrochloric acid (3.8 ml), and the mixture was stirred at 35°C for an hour. After addition of water (100 ml), the reaction mixture was adjusted to pH 5.5 with an aqueous sodium bicarbonate, followed by removal of the methanol. The residue was dissolved in ethyl acetate, washed with an aqueous sodium chloride and then dried over anhydrous magnesium sulfate, followed by treating with an activated charcoal. Removal of the solvent gave L - 2 - benzhydryloxycarbonyl - 2 - tert - butoxycarbonylaminoethyl 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - methoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (5.0 g).

I.R. (Nujol): 3370, 1775, 1730, 1616 cm^{-1}.

N.M.R. δ ppm (DMSO-d_6): 1.33, (9H, s), 3.83, 3.93 (2H, ABq, J=18Hz), 3.80 (3H, s), 4.47 (3H, broad s), 5.12 (1H, d, J=5Hz), 5.23 (1H, d, J=11Hz), 5.60 (1H, dd, J=5Hz, 8Hz), 5.66 (1H, d, J=18Hz), 6.70 (1H, s), 6.77 (1H, s), 6.8—7.2 (1H, m), 7.3 (10H, broad s), 9.57 (1H, d, J=8Hz).

Example 60

A solution of 7 - [2 - (2 - formamidoathiazol - 5 - yl) - 2 - methoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer) (1.9 g) and conc. hydrochloric acid (1.36 g) in methanol (190 ml) was stirred at ambient temperature for 1.3 hours. After the reaction mixture was evaporated to dryness, the residue was suspended in water (35 ml) and then adjusted to pH 7—8 with 10% aqueous sodium hydroxide, followed by adjusting to pH 3 with 10% hydrochloric acid. The precipitated solid was collected by filtration, washed with water and then dried to give 7 - [2 - (2 - aminothiazol - 5 - yl) - 2 - methoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer) (1.3 g), mp>250°C.

I.R. (Nujol): 3300, 1780, 1645, 1580, 1515 cm^{-1}.

N.M.R. δ ppm (DMSO-d_6): 3.76 (2H, q, J=20Hz), 3.81 (3H, s), 5.23 (1H, d, J=5Hz), 5.35 (1H, d, J=11Hz), 5.60 (1H, d, J=18Hz), 5.78 (1H, dd, J=5, 8Hz), 6.98 (1H, dd, J=11, 18Hz), 7.12 (1H, s), 7.60 (2H, broad s), 9.76 (1H, d, J=8Hz).

Example 61

7 - [2 - (2 - Aminothiazol - 5 - yl) - 2 - methoxyiminoacetoxyamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (anti isomer) (1.27 g) was obtained by reacting 7 - [2 - (2 - formamidothiazol - 5 - yl) - 2 - methoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (anti isomer) (2.1 g) with conc. hydrochloric acid (1.5 g) according to a similar manner to that of Example 60, mp>250°C.

I.R. (Nujol): 3320, 1775, 1655, 1575, 1515 cm^{-1}.

N.M.R. δ pm (DMSO-d_6): 3.76 (2H, q, J=20Hz), 4.01 (3H, s), 5.23 (1H, d, J=5Hz), 5.33 (1H, d, J=11Hz), 5.58 (1H, d, J=18Hz), 5.73 (1H, dd, J=5, 8Hz), 6.98 (1H, dd, J=11, 18Hz), 7.72 (2H, broad s), 7.79 (1H, s), 9.27 (1H, d, J=8Hz).

Example 62

7 - [2 - (2 - Aminothiazol - 4 - yl) - 2 - ethoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer) (12.2 g) was obtained by reacting 7 - [2 - (2 - formamidothiazol - 4 - yl) - 2 - ethoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer) (15.2 g) with conc. hydrochloric acid (14 ml) according to a similar manner to that of Example 60.

I.R. (Nujol): 3300, 1770, 1660, 1545 cm^{-1}.

N.M.R. δ ppm (DMSO-d_6): 1.27 (3H, t, J=7Hz), 3.77 (2H, q, J=18Hz), 4.17 (2H, q, J=7Hz), 5.23 (1H, d, J=5Hz), 5.35 (1H, d, J=11Hz), 5.62 (1H, d, J=17Hz), 5.83 (1H, dd, J=5Hz, 8Hz), 6.78 (1H, s), 6.98 (1H, dd, J=11Hz, 17Hz), 9.63 (1H, d, J=8Hz).

Example 63

7 - [2 - (2 - Aminothiazol - 4 - hexyloxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer) (2.1 g) mp 147—155°C (dec.), was obtained by reacting 7 - [2 - (2 - formamidothiazol - 4 - yl) - 2 - hexyloxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer) (3 g) with conc. hydrochloric acid (0.65 g) according to a similar manner to that of Example 60.

I.R. (Nujol): 3250, 1770, 1660, 1530 cm^{-1}.

N.M.R. δ ppm (DMSO-d_6): 0.84 (3H, t, J=6Hz), 1.03—2.0 (8H, m), 3.70 (2H, ABq, J≒18Hz), 4.07 (2H, t, J=6Hz), 5.20 (1H, d, J=5Hz), 5.28 (1H, d, J=11Hz), 5.55 (1H, d, J=17Hz), 5.77 (1H, dd, J=5Hz, 8Hz), 6.70 (1H, s), 6.93 (1H, dd, J=11Hz, 17Hz), 9.58 (1H, d, J=8Hz).

The following compounds were obtained by reacting 7-acylamino-3-vinyl cephalosporanic acid derivatives having formamido group with conc. hydrochloric acid according to a similar manner to that of Example 60.

Example 64

L - 2 - Amino - 2 - carboxyethyl 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - methoxyiminoacetamido] - 3 - vinyl - 3 - cepham - 4 - carboxylate (syn isomer).

I.R. (Nujol): 3200, 1770, 1735 (shoulder), 1650 (broad) cm^{-1}.

Example 65

7 - [2 - (2 - Aminothiazol - 4 - yl) - 2 - (L - 2 - amino - 2 - carboxyethoxycarbonylmethoxyimino)-acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer), mp 158°C (dec).

IR (Nujol): 3200 (broad), 1760 (broad) cm^{-1}.

Example 66

7 - [2 - (2 - Aminothiazol - 4 - yl) - 2 - (DL - 3 - amino - 3 - carboxypropoxyimino)acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer), mp 145°C (dec.).

I.R. (Nujol): 3120, 1766, 1612 cm^{-1}.

Example 67

A solution of benzhydryl 7 - [2 - (2 - formamidothiazol - 5 - yl) - 2 - methoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (2.7 g) in anisole (3.5 ml) and trifluoroacetic acid (10.8 ml) was stirred under ice-cooling for 15 minutes. The reaction mixture was poured into diisopropyl ether (140 ml), followed by stirring for 10 minutes. The precipitated solid was collected by filtration, washed with diisopropyl ether and then dried to give 7 - [2 - (2 - formamidothiazol - 5 - yl) - 2 - methoxyimino-acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer) (2.0 g), mp 147°C (dec.).

I.R. (Nujol): 3250, 3090, 1770, 1660, 1530 cm^{-1}.

N.M.R. δ ppm (DMSO-d_6): 3.78 (2H, q, J=18Hz), 3.92 (3H, s), 5.27 (1H, d, J=5Hz), 5.33 (1H, d, J=11Hz), 5.58 (1H, d, J=17Hz), 5.82 (1H, dd, J=5.8Hz), 6.97 (1H, dd, J=11, 17Hz), 7.57 (1H, s), 8.57 (1H, s), 9.89 (1H, d, J=8Hz).

Example 68

7 - [2 - (2 - Formamidothiazol - 5 - yl) - 2 - methoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (anti isomer) (2.35 g), mp 165°C (dec.), was obtained by reacting benzhydryl 7 - [2 - (2 - formamidothiazol - 5 - yl) - 2 - methoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (anti isomer) (3.0 g) with trifluoroacetic acid (12 ml) in the presence of anisole (3.9 ml) according to a similar manner to that of Example 67.

I.R. (Nujol): 3260, 1780, 1730, 1690, 1670, 1575, 1520 cm^{-1}.

N.M.R. δ ppm (DMSO-d_6): 3.75 (2H, q, J=18Hz), 4.14 (3H, s), 5.28 (1H, d, J=5Hz), 5.35 (1H, d, J=11Hz), 5.62 (1H, d, J=18Hz), 5.77 (1H, dd, J=5, 8Hz), 7.02 (1H, dd, J=11, 18Hz), 8.23 (1H, s), 8.60 (1H, s), 9.48 (1H, d, J=8Hz).

Example 69

7 - [2 - (2 - Formamidothiazol - 4 - yl) - 2 - ethoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer) (15.3 g) was obtained by reacting benzhydryl 7 - [2 - (2 - formamidothiazol - 4 - yl) - 2 - ethoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (24.7 g) with trifluoroacetic acid (45.6 g) in the presence of anisole (17 g) according to a similar manner to that of Example 67.

I.R. (Nujol): 3250, 1770, 1690, 1660, 1540 cm^{-1}.

N.M.R. δ ppm (DMSO-d_6): 1.30 (3H, t, J=7Hz), 3.77 (2H, q, J=17Hz), 4.22 (2H, q, J=7Hz), 5.27 (1H, d, J=5Hz), 5.36 (1H, d, J=11Hz), 5.62 (1H, d, J=17Hz), 5.88 (1H, dd, J=5Hz, 8Hz), 6.98 (1H, dd, J=11Hz, 17Hz), 7.43 (1H, s), 8.55 (1H, s), 9.70 (1H, d, J=8Hz), 12.47 (1H, broad s).

Example 70

7 - [2 - (2 - Formamidothiazol - 4 - yl) - 2 - hexyloxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer) (3.1 g) was obtained by reacting benzhydryl 7 - [2 - (2 - formamidothiazol - 4 - yl) - 2 - hexyloxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (5.5 g) with trifluoroacetic acid (9.3 g) in the presence of anisole (3.5 g) according to a similar manner to that of Example 67.

I.R. (Nujol): 3250, 1780, 1700, 1685 (shoulder), 1650, 1570, 1550 cm^{-1}.

N.M.R. δ ppm (DMSO-d_6): 0.88 (3H, t, J=6Hz), 1.07—2.0 (8H, m), 3.72 (2H, ABq, J=18Hz), 4.13 (2H, t, J=6Hz), 5.23 (1H, d, J=5Hz), 5.37 (1H, d, J=11Hz), 5.60 (1H, d, J=17Hz), 5.83 (1H, dd, J=5Hz, 8Hz), 6.97 (1H, dd, J=11Hz, 17Hz), 7.40 (1H, s), 8.53 (1H, s), 9.65 (1H, d, J=8Hz), 12.62 (1H, broad s).

The following compounds were obtained by reacting 7-acylamino-3-vinyl cephalosporanic acid derivatives having benzhydryloxycarbonyl with trifluoroacetic acid in the presence of anisole according to a similar manner to that of Example 67.

Example 71

7 - [2 - (2 - Aminothiazol - 5 - yl) - 2 - methoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer), mp>250°C.

IR (Nujol): 3300, 1780, 1645, 1580, 1515 cm^{-1}.

Example 72

7 - [2 - (2 - Aminothiazol - 5 - yl) - 2 - methoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (anti isomer), mp>250°C.

Example 73

7 - [2 - (2 - Aminothiazol - 4 - yl) - 2 - ethoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer).

IR (Nujol): 3300, 1770, 1660, 1545 cm^{-1}.

Example 74

7 - [2 - (2 - Aminothiazol - 4 - yl) - 2 - hexyloxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer), mp 147—155°C (dec.).

IR (Nujol): 3250, 1770, 1660, 1530 cm^{-1}.

Example 75

(1) 7 - [2 - (2 - Aminothiazol - 4 - yl) - 2 - carboxymethoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer) (1.8 g) and sodium bicarbonate (667 mg) were dissolved in water (40 ml) and the solution was lyphilized and then dried to prepare disodium salts of 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - carboxymethoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer) (1.9 g).

IR (Nujol): 3300 (broad), 3180 (broad), 1750, 1660, 1535 cm^{-1}.

NMR δ ppm (DMSO-d_6): 3.42 (2H, broad s), 4.37 (2H, broad s), 5.10 (1H, d, J=5Hz), 4.6—5.9 (3H, m), 6.89 (1H, s), 6.6—7.3 (1H, m) 7.33 (2H, broad s) mp>250°C.

(2) To a solution of the above product (1.8 g) in N,N-dimethylformamide (18 ml) was addeed iodomethyl pivalate (1.84 g) in N,N-dimethylformamide (1.8 ml) under ice-cooling, followed by stirring at the same temperature for 15 minutes. After the reaction mixture was poured into a mixture of ice-water and ethyl acetate, the organic layer was separated out. The remained aqueous layer was extracted with ethyl acetate and the combined ethyl acetate solution was washed with an aqueous sodium bicarbonate and an aqueous sodium chloride, followed by drying over anhydrous magnesium sulfate. Removal of the solvent gave a residue, which was pulverized with diisopropyl ether, followed by collecting by filtration to obtain pivaloyloxymethyl 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - (pivaloyloxymethoxycarbonylmethoxyimino)-acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (0.9 g), mp 115°C (dec.).

I.R. (Nujol): 3400, 3260, 3100, 1780, 1750, 1660, 1530 cm^{-1}.

N.M.R. δ ppm (DMSO-d_6): 1.06 (18H, s), 3.77 (2H, q, J=18Hz), 4.76 (2H, s), 5.25 (1H, d, J=5Hz), 5.4—6.1 (7H, m), 6.5—7.2 (1H, m), 6.82 (1H, s), 7.24 (2H, broad s), 9.59 (1H, d, J=8Hz).

Example 76

To a solution of sodium 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - methoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (2.2 g) in N,N-dimethylformamide (25 ml) was added dropwise a solution of iodomethyl acetate (1 g) in N,N-dimethylformamide (3 ml) below 5°C in the course of 2 minutes, and the mixture was stirred at the same temparature for 15 minutes. The reaction was poured into a mixture of water (100 ml) and ethyl acetate (50 ml), and the separated aqueous solution was extracted with ethyl acetate (30 ml). The combined ethyl acetate solution was washed twice with 5% aqueous sodium bicarbonate and twice with an aqueous sodium chloride, and then dried over anhydrous magnesium sulfate. Removal of the solvent gave a residue, which was pulverized with diisopropyl ether and collected by filtration to obtain acetoxymethyl 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - methoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (1.6 g), mp 78—83°C.

I.R. (Nujol): 3300, 1765 (broad), 1660, 1610, 1535 cm^{-1}.

N.M.R. δ ppm (DMSO-d_6): 2.10 (3H, s), 3.77 (2H, ABq, J=18Hz), 3.87 (3H, s), 5.25 (1H, d, J=5Hz), 5.38 (1H, d, J=11Hz), 5.67 (1H, d, J=17Hz), 5.85 (3H, m), 6.77 (1H, s), 6.90 (1H, dd, J=11Hz, 17Hz), 9.80 (1H, d, J=8Hz).

Example 77

Propionyloxymethyl 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - methoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (1.5 g), mp 79—85°C, was obtained by reacting sodium 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - methoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (1.5 g) with iodomethyl propionate (0.82 g) according to a similar manner to that of Example 76.

I.R. (Nujol): 3350, 1770 (broad), 1650, 1620, 1530 cm^{-1}.

N.M.R. δ ppm (DMSO-d_6): 1.03 (3H, t, J=7Hz), 2.40 (2H, q, J=7Hz), 3.77 (2H, ABq, J=17Hz), 3.85 (3H, s), 5.38 (1H, d, J=11Hz), 5.62 (1H, d, J=17Hz), 5.85 (3H, m), 6.75 (1H, s), 6.85 (1H, dd, J=11Hz, 17Hz), 9.62 (1H, d, J=8Hz).

Example 78

Isobutyryloxymethyl 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - methoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (2.3 g), mp 92—100°C (dec.), was obtained by reacting sodium 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - methoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (3.0 g) with iodomethyl isobutyrate (1.7 g) according to a similar manner to that of Example 76.

I.R. (Nujol): 3400—3100, 1780—1740, 1670, 1610, 1530 cm^{-1}.

N.M.R. δ ppm (DMSO-d_6): 1.1 (6H, d, J=6Hz), 2.3—2.9 (1H, m), 3.46—4.23 (2H, m), 3.85 (3H, s), 5.25 (1H, d, J=5Hz), 5.38 (1H, d, J=11Hz), 5.52—6.0 (2H, m), 5.87 (2H, s), 6.77 (1H, s), 6.85 (1H, dd, J=11Hz, 17Hz), 9.63 (1H, d, J=8Hz).

Example 79

Pivaloyloxymethyl 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - ethoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (2.6 g) was obtained by reacting sodium 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - ethoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (3.56 g) with iodomethyl pivalate (1.94 g) according to a similar manner to that of Example 76.

I.R. (Nujol): 3300, 1780, 1740, 1670, 1610, 1530 cm^{-1}.

N.M.R. δ ppm (DMSO-d_6): 1.17 (9H, s), 1.23 (3H, t, J=6Hz), 3.77 (2H, q, J=17Hz), 4.12 (2H, q, J=6Hz), 5.23 (1H, d, J=5Hz), 5.38 (1H, d, J=11Hz), 5.62 (1H, d, J=17Hz), 5.73 (3H, m), 6.73 (1H, s), 6.83 (1H, dd, J=11Hz, 17Hz), 9.57 (1H, d, J=8Hz).

The following compound was obtained according to a similar manner to that of Example 76.

Example 80

L - 2 - Benzhydryloxyloxycarbonyl - 2 - tert - butoxycarbonylaminoethyl 7 - [2 - (2 - formamidothiazol - 4 - yl) - 2 - methoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer).

I.R. (Nujol): 3280, 1782, 1709, 1689, 1656 cm^{-1}.

Example 81

To a solution of sodium 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - methoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (2.0 g) in N,N-dimethylformamide (40 ml) was added sodium iodide (0.8 g) and 1 - bromopropyl acetate (0.9 g) under ice-cooling with stirring, and the stirring was continued at the same temperature for half an hour. The reaction mixture was poured into a mixture of water and ethyl acetate, and the separated organic solution was washed twice with a saturated aqueous sodium chloride and twice with water, followed by drying over anhydrous magnesium sulfate. Removal of the solvent gave a residue, which was pulverized with diisopropyl ether and then chromatographed on silica gel eluting with a mixed solvent of ethyl acetate and chloroform (4:6 to 6:4 by volume), and fractions containing a desired compound were collected. Removal of the solvent gave a residue, which was pulverized with diisopropyl ether and then collected by filtration to obtain 1 - acetoxypropyl 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - methoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (0.62 g), mp 97—101°C.

I.R. (Nujol): 3300, 1765, 1670, 1610 cm^{-1}.

N.M.R. δ ppm (DMSO-d_6): 0.95 (3H, m), 1.87 (2H, m), 2.07 (3H, s), 3.48—4.23 (2H, m), 3.85 (3H, s), 5.25 (1H, d, J=4.0Hz), 5.25—5.98 (3H, m), 6.74 (1H, s), 6.53—7.38 (4H, m), 9.58 (1H, d, J=8.0Hz).

Example 82

A solution of benzhydryl 7 - (4 - bromo - 2 - methoxyiminoacetoacetamido) - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (1.2 g), thiourea (0.5 g) and sodium acetate (trihydrate) (0.7 g) in water (20 ml) and tetrahydrofuran (20 ml) was stirred at 30°C for 3.5 hours. The reaction mixture was extracted with ethyl acetate, and the extract was washed with water and dried over anhydrous magnesium sulfate. Removal of the solvent gave a residue, which was pulverized with diethyl ether to obtain benzhydryl 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - methoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (1.05 g).

I.R. (Nujol): 3230, 1780, 1710, 1650, 1620, 1580, 1540 cm^{-1}.

N.M.R. δ ppm (DMSO-d_6): 3.78 (2H, q, J=17Hz), 3.87 (3H, s), 5.28 (1H, d, J=5Hz), 5.32 (1H, d, J=11Hz), 5.65 (1H, d, J=17Hz), 5.72 (1H, dd, J=5Hz, 8Hz), 6.80 (1H, s), 6.80 (1H, dd, J=11Hz, 17Hz), 6.97 (1H, s), 7.20—7.67 (10H, m), 9.67 (1H, d, J=8Hz).

Example 83

7 - [2 - (2 - Aminothiazol - 4 - yl) - 2 - methoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer) (0.8 g) was obtained by reacting 7 - (4 - bromo - 2 - methoxyiminoacetoacetamido) - 3 - vinyl-3 - cephem - 4 - carboxylic acid (syn isomer) (1.5 g) with thiourea (0.8 g) according to a similar manner to that of Example 82.

I.R. (Nujol): 3400—3100, 1780, 1660, 1630, 1540 cm^{-1}.

N.M.R. δ ppm (DMSO-d_6): 3.72 (2H, q, J=18Hz), 3.87 (3H, s), 5.20 (1H, d, J=5Hz), 5.33 (1H, d, J=11Hz), 5.58 (1H, d, J=18Hz), 5.78 (1H, dd, J=5Hz, 8Hz), 6.77 (1H, s), 6.95 (1H, dd, J=11Hz, 18Hz), 9.62 (1H, d, J=8Hz).

The following compounds were obtained by reacting the corresponding 7 - acylamino - 3 - vinyl cephalosporanic acid derivatives with thiourea according to a similar manner to that of Example 82.

Example 84

L - 2 - Benzhydryloxycarbonyl - 2 - tert - butoxycarbonylaminoethyl 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - methoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer).

I.R. (Nujol): 3370, 1775, 1730, 1616 cm^{-1}.

Example 85

7 - [2 - (2 - Aminothiazol - 4 - yl) - 2 - ethoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer).

I.R. (Nujol): 3300, 1770, 1660, 1545 cm^{-1}.

Example 86

7 - [2 - (2 - Aminothiazol - 4 - yl) - 2 - hexyloxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer), mp 147—155°C (dec.).

I.R. (Nujol): 3250, 1770, 1660, 1530 cm^{-1}.

Example 87

Pivaloyloxymethyl 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - (pivaloyloxymethoxycarbonylmethoxyimino)-acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer), mp 115°C (dec.).

I.R. (Nujol): 3400, 3260, 3100, 1780, 1750, 1660, 1530 cm^{-1}.

Example 88

Acetoxymethyl 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - methoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer), mp 78—83°C.

I.R. (Nujol): 3300, 1765 (broad), 1660, 1610; 1535 cm^{-1}.

Example 89

Propionyloxymethyl 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - methoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer), mp 79—85°C.

I.R. (Nujol): 3350, 1770 (broad), 1650, 1620, 1530 cm^{-1}.

Example 90

Isobutyryloxymethyl 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - methoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer), mp 92—100°C (dec.).

I.R. (Nujol): 3400—3100, 1780—1740, 1670, 1610, 1530 cm^{-1}.

Example 91

Pivaloyloxymethyl 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - ethoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer).

I.R. (Nujol): 3300, 1780, 1740, 1670, 1610, 1530 cm^{-1}.

Example 92

1 - Acetoxypropyl 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - methoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer), mp 97—101°C.

I.R. (Nujol): 3300, 1765, 1670, 1610 cm^{-1}.

Example 93

To a mixture of trifluoroacetic acid (28.8 ml) and anisole (4.8 ml) was added L - 2 - benzhydryloxycarbonyl - 2 - tert - butoxycarbonylaminoethyl 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - methoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (4.8 g) at 5°C, and the mixture was stirred at 0 to 5°C for half an hour. The reaction mixture was added dropwise to diisopropyl ether (900 ml), and the precipitated material was collected by filtration, and thereto were added water (100 ml) and ethyl acetate (100 ml). The separated aqueous solution was washed with ethyl acetate (50 ml), followed by completely removing the ethyl acetate therein by evaporation. The resultant aqueous solution was adjusted to pH 3.0 with 5% aqueous sodium bicarbonate, followed by removal of the precipitated material. The aqueous solution was chromatographed on a nonionic adsorption resin, "Diaion HP—20" (Trade Mark, manufactured by Mitsubishi Chemical Industries Ltd.) (100 ml). After washing with water (300 ml), elution was carried out with 30% aqueous isopropyl alcohol and fractions containing a desired compound were collected. Removal of the solvent gave a residue, which was lyophilized and then dried to obtain L - 2 - amino - 2 - carboxyethyl 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - methoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (1.5 g).

I.R. (Nujol): 3200, 1770, 1735 (shoulder), 1650 (broad) cm^{-1}.

N.M.R.δ ppm (DCl+D_2O): 3.73, 3.94 (2H, ABq, J=18Hz), 4.13 (3H, s), 4.5—4.9 (3H, m), 5.30 (1H, d, J=5Hz), 5.56 (1H, d, J=11Hz), 5.77 (1H, d, J=18Hz), 5.80 (1H, d, J=5Hz), 7.11 (1H, dd, J=11Hz, 18Hz), 7.19 (1H, s).

Example 94

A mixture of benzhydryl 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - (L - 2 - benzhydryloxycarbonyl - 2 - tert - butoxycarbonylaminoethoxycarbonylmethoxyimino)acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (5.4 g), trifluoroacetic acid (21.6 ml) and anisole (5.4 ml) was stirred at 5 to 10°C for 70 minutes. The reaction mixture was added dropwise to diisopropyl ether (1000 ml), followed by collecting the precipitated material. After washing with diisopropyl ether, said material was dissolved in a mixture of ethyl acetate (50 ml) and water (50 ml). The separated aqueous solution was washed with ethyl acetate, and the ethyl acetate therein was completely removed by evaporation. The resultant aqueous solution was adjusted to pH 3.0 with 5% sodium bicarbonate and then chromatographed on a nonionic adsorption resin, "Diaion HP—20" (100 ml). After washing with water (300 ml), elution was carried out 20% aqueous isopropyl alcohol, and fractions containing a desired compound were collected. Removal of the solvent gave a residue, which was lyophilized to obtain 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - (L - 2 - amino - 2 - carboxyethoxycarbonylmethoxyimino)acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer) (1.7 g), mp 158°C (dec.).

I.R. (Nujol): 3200 (broad), 1760 (broad) cm^{-1}.

N.M.R. δ ppm (DMSO-d_6): 3.51, 3.75 (2H, ABq, J=18Hz), 4.3—4.8 (5H, m), 5.13 (1H, d, J=5Hz), 5.19 (1H, d, J=11Hz), 5.44 (1H, d, J=18Hz), 5.72 (1H, dd, J=5Hz, 8Hz), 6.79 (1H, s), 6.93, (1H, dd, J=11Hz, 18Hz), 9.66 (1H, d, J=8Hz).

Example 95

A mixture of benzhydryl 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - (DL - 3 - benzhydryloxycarbonyl - 3 - tert - butoxycarbonylamino)acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (3.3 g), trifluoroacetic acid (20 ml) and anisole (3.3 ml) was stirred at 5 to 10°C for 1.5 hours. The reaction mixture was added dropwise to diisopropyl ether (300 ml), and the precipitated material was collected by filtration and then washed with diisopropyl ether, followed by dissolving in water (50 ml). The aqueous solution was washed with ethyl acetate (50 ml × 2), and the ethyl acetate therein was completely removed by evaporation. The resultant aqueous solution was adjusted to pH 3.1 with 5% aqueous sodium bicarbonate and chromatographed on a nonionic adsorption resin, "Diaion HP—20" (100 ml). After washing with water (300 ml), elution was carried out with 20% aqueous isopropyl alcohol, and the fractions containing a desired compound were collected and then treated with an activated charcoal. Removal of the solvent gave a residue, which was lyophilized to obtain 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - (DL - 3 - amino - 3 - carboxypropoxyimino)acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer) (0.7 g), mp 145°C (dec.).

I.R. (Nujol): 3120, 1766, 1612 cm^{-1}.

N.M.R. δ ppm (D_2O+DCl): 2.53 (2H, m), 3.82 (2H, broad s), 4.31 (1H, t, J=6Hz), 4.57 (2H, t, J=6Hz), 5.32 (1H, d, J=5Hz), 5.53 (1H, d, J=11Hz), 5.73 (1H, d, J=18Hz), 5.82 (1H, d, J=5Hz), 7.13 (1H, dd, J=11Hz, 18Hz), 7.25 (1H, s).

Example 96

To a suspension of Vilsmeier reagent, which was prepared from N,N-dimethylformamide (1.8 g) and phosphorus oxychloride (3.7 g), in tetrahydrofuran (60 ml) was added 2 - (2 - formamidothiazol - 4 - yl) - 2 - (2 - pyridylmethoxyimino)acetic acid (syn isomer) (6.74 g) under ice-cooling with stirring, and the stirring

was continued at the same temperature for 30 minutes to prepare the activated acid solution. This solution was added to a solution of benzhydryl 7 - amino - 3 - vinyl - 3 - cephem - 4 - carboxylate hydrochloride (8.6 g) and trimethylsilylacetamide (15.7 g) in ethyl acetate (100 ml) at −20°C, and the mixture was stirred at −20 to −5°C for 2 hours. To the reaction mixture were added ethyl acetate and water, followed by separating the ethyl acetate layer. After the ethyl acetate solution was washed with a saturated aqueous sodium bicarbonate and an aqueous sodium chloride, it was dried over anhydrous magnesium sulfate. Removal of the solvent gave a residue, which was pulverized with diisopropyl ether to obtain benzhydryl 7 - [2 - (2 - formamidothiazol - 4 - yl) - 2 - (2 - pyridylmethoxyimino)acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (13.6 g).

I.R. (Nujol): 3250, 1760, 1720, 1660, 1580, 1560, 1540 cm^{-1}.

N.M.R. δ ppm (DMSO-d_6): 3.77 (2H, q, J=18Hz), 5.33 (4H, m), 5.63 (1H, d, J=17Hz), 6.03 (1H, dd, J=5Hz, 8Hz), 6.80 (1H, dd, J=11Hz, 17Hz), 7.00 (1H, s), 7.13—8.00 (14H, m), 8.53 (1H, m), 8.53 (1H, s). 10.07 (1H, d, J=8Hz), 12.7 (1H, s).

Example 97

Benzhydryl 7 - [2 - (2 - formamidothiazol - 4 - yl) - 2 - (3 - pyridylmethoxyimino)acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (8.7 g) was obtained by reacting benzhydryl 7 - amino - 3 - vinyl - 3 - cephem - 4 - carboxylate hydrochloride (8.6 g) with 2 - (2 - formaminothiazol - 4 - yl) - 2 - (3 - pyridylmethoxyimino)acetic acid (syn isomer) (6.74 g) according to a similar manner to that of Example 96.

I.R. (Nujol): 32.60, 1770, 1710, 1690, 1650, 1580, 1570, 1530 cm^{-1}.

N.M.R. δ ppm (DMSO-d_6): 3.75 (2H, q, J=18Hz), 5.27 (2H, s), 5.30 (1H, d, J=11Hz), 5.30 (1H, d, J=11Hz), 5.67 (1H, d, J=17Hz), 5.97 (1H, dd, J=5Hz, 8Hz), 6.78 (1H, dd, J=11Hz, 17Hz), 6.97 (1H, s), 7.20—7.67 (12H, m), 7.87 (1H, m), 8.53 (1H, s), 8.47—8.70 (2H, m), 9.88 (1H, d, J=8Hz), 12.67 (1H, broad s).

Example 98

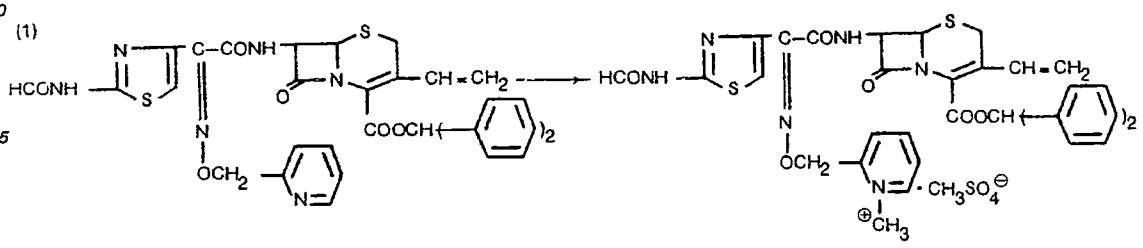
A mixture of benzhydryl 7 - [2 - (2 - formamidothiazol - 4 - yl) - 2 - (2 - pyridylmethoxyimino)acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (5.45 g), conc. hydrochloric acid (5 ml) and methanol (150 ml) was stirred at ambient temperature for 1.5 hours. After removal of the solvent, to the residue were added ethyl acetate and water, followed by adjusting to pH 7 with 20% aqueous sodium carbonate. The separated ethyl acetate solution was washed with an aqueous sodium chloride and then dried over anhydrous magnesium sulfate. Removal of the solvent gave benzhydryl 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - (2 - pyridylmethoxyimino)acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (4.6 g).

I.R. (Nujol): 32.40, 1775, 1720, 1670, 1610, 1590, 1540 cm^{-1}.

N.M.R. δ ppm (DMSO-d_6): 3.73 (2H, q, J=17Hz), 5.28 (2H, s), 5.28 (2H, m), 5.63 (1H, d, J=17Hz), 5.98 (1H, dd, J=5Hz, 8Hz), 6.82 (1H, dd, J=11Hz, 17Hz), 6.85 (1H, s), 7.00 (1H, s), 7.1—8.00 (13H, m), 8.53 (1H, dd, J=2Hz, 6Hz), 10.00 (1H, d, J=8Hz).

Example 99

(1)

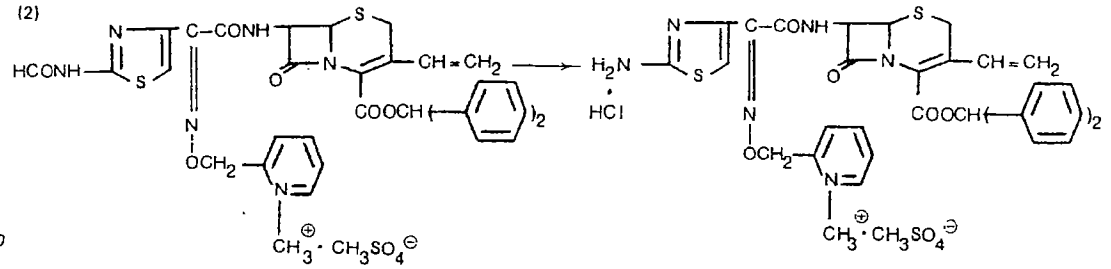


Benzhydryl 7 - [2 - (2 - formamidothiazol - 4 - yl) - 2 - (2 - pyridylmethoxyimino)acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (2.72 g) was added to a solution of dimethylsulfate (0.95 g) in tetrahydrofuran (120 ml), and the mixture was stirred at 43 to 46°C for 25 hours. After removal of the solvent, the residue was dissolved in a mixture of water (30 ml), tetrahydrofuran (30 ml) and ethyl acetate (50 ml), followed by separating an aqueous layer. The remaining organic solution was extracted with water, and ethanol was added to the combined aqueous solution. Removal of the solvent gave a residue, which was washed with a mixture of ethanol and diethyl ether to obtain 1 - methyl - 2 - [1 - (2 - formamidothiazol - 4 - yl) - 1 - {N - (4 - benzhydryloxycarbonyl - 3 - vinyl - 3 - cephem - 7 - yl) - carbamoyl} - methyleneaminooxymethyl]pyridinium methylsulfate (syn isomer) (1.7 g).

I.R. (Nujol): 3180, 1770, 1710, 1670, 1625, 1540 cm^{-1}.

N.M.R. δ ppm (DMSO-d_6): 3.40 (3H, s), 3.73 (2H, m), 4.38 (3H, s), 5.33 (1H, d, J=5Hz), 5.35 (1H, d, J=11Hz), 5.65 (1H, d, J=17Hz), 5.75 (2H, s), 6.02 (1H, dd, J=5Hz, 8Hz), 6.80 (1H, dd, J=11Hz, 17Hz), 6.98 (1H, s), 7.2—7.70 (10H, m), 7.57 (1H, s), 8.55 (1H, s), 7.93—8.63 (3H, m), 9.13 (1H, dd, J=2Hz, 6Hz), 10.00 (1H, d, J=8Hz).

(2)



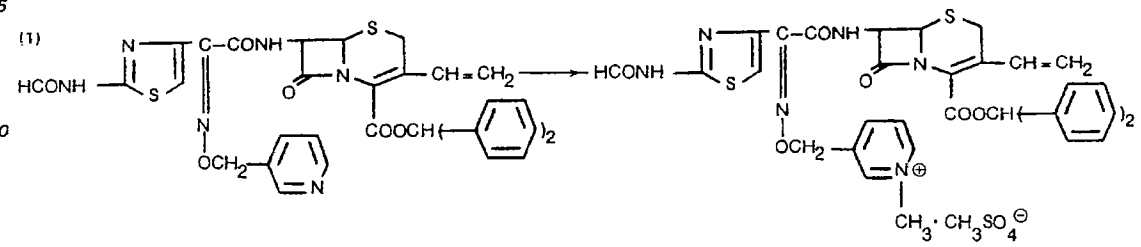
A solution of the object compound (1.6 g) obtained above and conc. hydrochloric acid (1 ml in methanol (30 ml) and tetrahydrofuran (20 ml) was stirred at ambient temperature for 5 hours. After removal of the solvent, the residue was dissolved in tetrahydrofuran and ethanol, followed by concentration to give a residue, which was pulverized with diethyl ether to obtain hydrochloride of 1 - methyl - 2 - (1 - (2 - aminothiazol - 4 - yl) - 1 - {N - (4 - benzhydryloxycarbonyl - 3 - vinyl - 3 - cephem - 7 - yl)carbamoyl} - methyleneaminooxymethyl]pyridinium methylsulfate (syn isomer) (1.5 g).

I.R. (Nujol): 1780, 1720, 1680, 1630, 1585, 1545, 1500 cm^{-1}.

N.M.R. δ ppm (DMSO-d_6): 3.43 (3H, s), 3.80 (2H, m), 4.40 (3H, s), 5.33 (1H, d, J=5Hz), 5.33 (1H, d, J=11Hz), 5.57 (1H, d, J=17Hz), 5.73 (2H, s), 5.83 (1H, dd, J=5Hz, 8Hz), 6.82 (1H, dd, J=11Hz, 17Hz), 6.97 (1H, s), 7.07 (1H, s), 7.17—7.67 (10H, m), 7.93—8.80 (3H, m), 9.17 (1H, dd, J=2Hz, 6Hz), 10.08 (1H, d, J=8Hz).

Example 100

(1)

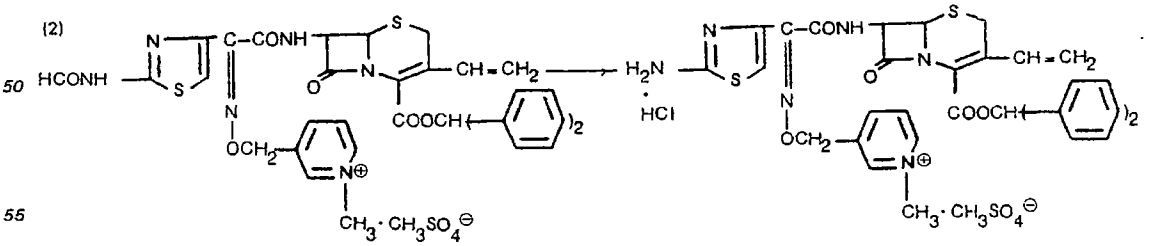


1 - Methyl - 3 - [1 - (2 - formamidothiazol - 4 - yl) - 1 - {N - (4 - benzhydryloxycarbonyl - 3 - vinyl - 3 - cephem - 7 - yl)carbamoyl} - methyleneaminooxymethyl]pyridinium methylsulfate (syn isomer) (2.6 g) was obtained by reacting benzhydryl 7 - [2 - (2 - formamidothiazol - 4 - yl) - 2 - (3 - pyridylmethoxyimino)acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (3.4 g) with dimethylsulfate (1.26 g) according to a similar manner to that of Example 99—(1).

I.R. (Nujol): 1770, 1720, 1670, 1550 cm^{-1}.

N.M.R. δ ppm (DMSO-d_6): 3.42 (3H, s), 3.80 (2H, m), 4.40 (3H, s), 5.33 (1H, d, J=5Hz), 5.38 (1H, d, J=11Hz), 5.52 (2H, s), 5.70 (1H, d, J=17Hz), 5.95 (1H, dd, J=5Hz, 8Hz), 6.82 (1H, dd, J=11Hz, 17Hz), 7.00 (1H, s), 7.13—7.67 (10H, m), 7.58 (1H, s), 8.17 (1H, m), 8.57 (1H, s), 8.67 (1H, m), 9.03 (1H, m), 9.03 (1H, s), 9.95 (1H, d, J=8Hz).

(2)



Hydrochloride of 1 - methyl - 3 - [1 - (2 - aminothiazol - 4 - yl) - 1 - {N - (4 - benzhydryloxycarbonyl - 3 - vinyl - 3 - cephem - 7 - yl)carbamoyl} - methyleneaminooxymethyl]pyridinium methylsulfate (syn isomer) (1.1 g) was obtained by reacting the object compound (1.5 g) obtained above with conc. hydrochloric acid (1.2 ml) according to a similar manner to that of Example 94—(2).

I.R. (Nujol): 3400—3100, 1760, 1660, 1600, 1530 cm^{-1}.

N.M.R. δ ppm (DMSO-d_6): 3.40 (3H, s), 3.73 (2H, broad s), 4.45 (3H, s), 5.20 (1H, d, J=5Hz), 5.38 (1H, d, J=11Hz), 5.47 (2H, s), 5.63 (1H, d, J=17Hz), 5.80 (1H, dd, J=5Hz, 8Hz), 6.7—7.7 (11H, m), 6.97 (1H, s), 7.12 (1H, s), 8.17 (1H, m), 8.7 (1H, m), 9.00 (1H, m), 9.17 (1H, broad s), 10.02 (1H, d, J=8Hz).

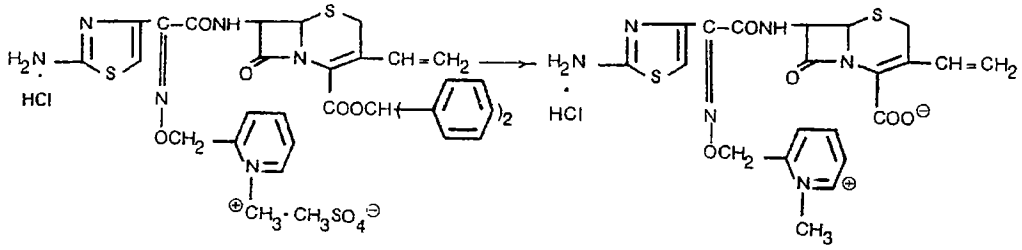
Example 101

To a solution of benzhydryl 7-[2-(2-aminothiazol-4-yl)-2-(2-pyridylmethoxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylate (syn isomer) (4.6 g) in methylene chloride (20 ml) and anisole (3.0 g) was added trifluoroacetic acid (11.2 g) under ice-cooling with stirring, and the stirring was continued at ambient temperature for 1.5 hours. The reaction mixture was added dropwise to diisopropyl ether (300 ml) and the precipitated crystals were collected by filtration, followed by suspending in water (70 ml). After adjusting to pH 7.5 with 1N aqueous sodium hydroxide, the resultant aqueous solution was washed with ethyl acetate. The aqueous solution was further adjusted to pH 3.4 with 10% hydrochloric acid, followed by collecting the precipitated crystals to obtain 7-[2-(2-aminothiazol-4-yl)-2-(2-pyridylmethoxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid (syn isomer) (1.8 g).

I.R. (Nujol): 3300, 1770, 1650, 1620 (shoulder), 1540 cm^{-1}.

N.M.R. δ ppm (DMSO-d_6): 3.70 (2H, q, J=18Hz(, 5.23 (1H, d, J=5Hz), 5.30 (2H, s), 5.32 (1H, d, J=11Hz), 5.60 (1H, d, J=17Hz), 5.85 (1H, dd, J=5Hz, 8Hz), 6.82 (1H, dd, J=11Hz, 17Hz), 6.82 (1H, s), 7.00—8.10 (3H, m), 8.57 (1H, d, J=4Hz), 9.97 (1H, d, J=8Hz).

Example 102

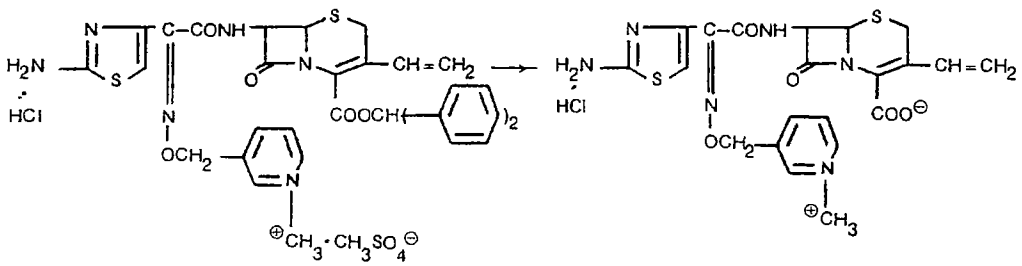


Hydrochloride of 1 - methyl - 2 - [1 - (2 - aminothiazol - 4 - yl) - 1 - {N - (4 - benzhydryloxycarbonyl - 3 - vinyl - 3 - cephem - 7 - yl)carbamoyl} - methyleneaminooxymethyl]pyridinium methylsulfate (syn isomer) (2.6 g) was suspended in methylene chloride (20 ml) and ainsole (1.4 g), and thereto was added trifluoroacetic acid (5.8 g) under ice-cooling with stirring, followed by stirring at ambient temperature for 1.5 hours. After the reaction mixture was added dropwise to diisopropyl ether (250 ml), the precipitated materials were collected by filtration and dissolved in water (20 ml). The aqueous solution was adjusted to pH 6.5 with 1N aqueous sodium hydroxide and washed with ethyl acetate, and then adjusted to pH 2 with 10% hydrochloric acid, followed by subjecting to column chromatography on nonionic adsorption resin "Diaion HP—20" (100 ml). After washing with water, elution was carried out with 30% aqueous isopropyl alcohol, and fractions containing a desired compound were collected and evaporated. The residue obtained was lyophilized to obtain hydrochloride of 7 - [2 - aminothiazol - 4 - yl) - 2 - {(1 - methyl - 2 - pyridinio)methoxyimino} - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (1.2 g).

I.R. (Nujol): 1770, 1720, 1670, 1630, 1540 cm^{-1}.

N.M.R. δ ppm (D_2O): 3.60 (2H, broad s), 4.38 (3H, s), 5.22 (1H, d, J=5Hz), 5.25 (1H, d, J=11Hz), 5.40 (1H, d, J=17Hz), 5.70 (2H, s), 5.82 (1H, d, J=5Hz), 6.82 (1H, dd, J=11Hz, 17Hz), 7.03 (1H, s), 7.80—8.73 (3H, m), 8.87 (1H, dd, J=2Hz, 6Hz).

Example 103



Hydrochloride of 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - {(1 - methyl - 3 - pyridinio)methoxyimino} - acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (0.4 g) was obtained by reacting hydrochloride of 1 - methyl - 3 - [1 - (2 - aminothiazol - 4 - yl) - 1 - {N - (4 - benzhydryloxycarbonyl - 3 - vinyl - 3 - cephem - 7 - yl)carbamoyl} - methyleneaminooxymethyl]pyridinium methylsulfate (syn

isomer) (1.0 g) with trifluoroacetic acid (2.8 g) in the presence of anisole (0.52 g) according to a similar manner to that of Example 102.

I.R. (Nujol): 3400—3100, 1760, 1660, 1600, 1530 cm^{-1}.

N.M.R. δ ppm (D_2O): 3.67 (2H, broad s), 4.43 (3H, s), 5.25 (1H, d, J=5Hz), 5.30 (1H, d, J=11Hz), 5.43 (1H, d, J=17Hz), 5.50 (2H, s), 5.80 (1H, d, J=5Hz), 6.83 (1H, dd, J=11Hz, 17Hz), 7.02 (1H, s), 8.10 (1H, m), 8.78—8.90 (2H, m), 8.90 (1H, s).

Example 104

Benzhydryl 7 - [2 - (2 - formamidothiazol - 4 - yl) - 2 - (1 - tert - butoxycarbonyl - 1 - methylethoxyimino)acetamido) - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (4.93 g) was obtained by reacting benzhydryl 7-amino-3-vinyl-3-cephem-4-carboxylate hydrochloride (3.2 g) with 2-(2-formamidothiazol-4-yl)-2-(1-tert-butoxycarbonyl-1-methylethoxyimino)acetic acid (syn isomer) (2.9 g) according to a similar manner to that of Example 37.

I.R. (Nujol): 3150, 1780, 1720, 1690 cm^{-1}.

N.M.R. δ ppm (DMSO-d_6): 1.27—1.81 (15H, m), 3.81 (2H, q, J=18.0Hz), 5.34 (1H, d, J=4.0Hz), 5.22—6.18 (3H, m), 6.79 (1H, dd, J=12.0Hz, 18.0Hz), 7.00 (1H, s), 7.13—7.75 (11H, m), 8.54 (1H, s), 9.58 (1H, d, J=8.0Hz).

Example 105

Benzhydryl 7-[2-(2-formamidothiazol-4-yl)-2-(1-tert-butoxycarbonylethoxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylate (syn isomer) (5.62 g) was obtained by reacting benzhydryl 7-amino-3-vinyl-3-cephem-4-carboxylate hydrochloride (3.4 g) with 2-(2-formamidothiazol-4-yl)-2-(1-tert-butoxycarbonylethoxyimino)acetic acid (syn isomer) (3.0 g) according to a similar manner to that of Example 37.

I.R. (Nujol): 3250, 3150, 1780, 1720, 1680 cm^{-1}.

N.M.R. δ ppm (DMSO-d_6): 1.23—1.72 (12H, m), 3.78 (2H, q, J=18.0Hz), 4.66 (1H, q, J=8.0Hz), 5.33 (1H, d, J=5.0Hz), 3.27—6.16 (1H, m), 6.79 (1H, dd, J=10.0Hz, 18.0Hz), 6.98 (1H, s), 7.18—7.82 (11H, m), 8.56 (1H, s), 9.59 (d, J=8.0Hz) } (1H)
9.67 (d, J=8.0Hz) }

Example 106

Benzhydryl 7-[2-(2-formamidothiazol-4-yl)-2-ethoxycarbonylmethoxyiminoacetamido)-3-vinyl-3-cephem-4-carboxylate (syn isomer) (6.4 g) was obtained by reacting benzhydryl 7-amino-3-vinyl-3-cephem-4-carboxylate hydrochloride (4.29 g) with 2-(2-formamidothiazol-4-yl)-2-ethoxycarbonylmethoxyiminoacetic acid (syn isomer) (3.3 g) according to a similar manner to that of Example 37.

I.R. (Nujol): 3250, 1780, 1710, 1690, 1660, 1540 cm^{-1}.

N.M.R. δ ppm (DMSO-d_6): 1.20 (3H, t, J=7Hz), 3.77 (2H, m), 4.15 (2H, q, J=7Hz), 4.75 (2H, s), 5.28 (1H, d, J=11Hz), 5.30 (1H, d, J=5Hz), 5.65 (1H, d, J=17Hz), 5.97 (1H, dd, J=5Hz, 8Hz), 6.82 (1H, dd, J=11Hz, 17Hz), 6.97 (1H, s), 7.17—7.67 (11H, m), 8.55 (1H, s), 9.73 (1H, d, J=8Hz), 12.67 (1H, broad, s).

Example 107

7 - [2 - (2 - Formamidothiazol - 4 - yl) - 2 - tert - butoxycarbonylmethoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer) (2.7 g) was obtained by reacting 7-amino-3-vinyl-3-cepham-4-carboxylic acid (2.26 g) with 2-(2-formamidothiazol-4-yl)-2-tert-butoxycarbonylmethoxyiminoacetic acid (syn isomer) (3.29 g) according to a similar manner to that of Example 37.

I.R. (Nujol): 3230, 1780, 1720, 1680, 1542 cm^{-1}.

N.M.R. δ ppm (DMSO-d_6): 1.45 (9H, s), 3.73 (2H, q, J=18Hz), 4.63 (2H, s), 5.23 (1H, d, J=5Hz), 5.30 (1H, d, J=11Hz), 5.58 (1H, d, J=18Hz), 5.85 (1H, dd, J=5Hz, 8Hz), 6.98 (1H, dd, J=11Hz, 18Hz), 7.46 (1H, s), 8.53 (1H, s), 9.63 (1H, d, J=8Hz), 12.73 (1H, broad s).

Example 108

Benzhydryl 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - (1 - tert - butoxycarbonyl - 1 - methylethoxyimino)acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) 4.03 g) was obtained by reacting benzhydryl 7 - [2 - (2 - formamidothiazol - 4 - yl) - 2 - (1 - tert - butoxycarbonyl - 1 - methylethoxyimino)acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (4.8 g) with conc. hydrochloric acid (1.4 g) according to a similar manner to that of Example 57.

I.R. (Nujol): 3260, 1780, 1720, 1680, 1620 cm^{-1}.

N.M.R. δ ppm (DMSO-d_6): 1.21—1.70 (15H, m), 3.83 (2H, m), 5.30 (1H, d, J=4.0Hz), 5.16—6.10 (2H, m), 6.94 (1H, dd, J=4.0Hz, 8.0Hz), 6.44—7.04 (1H, m), 6.74 (1H, s), 6.96 (1H, s), 7.07—7.66 (10H, m), 9.41 (1H, d, J=8.0Hz).

Example 109

Benzhydryl 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - (1 - tert - butoxycarbonylethoxyimino)-acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (4.81 g) was obtained by reacting benzhydryl 7 - [2 - (2 - formamidothiazol - 4 - yl) - 2 - (1 - tert - butoxycarbonylethoxyimino)-

acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (5.5 g) with conc. hydrochloric acid (1.6 g) according to a similar manner to that of Example 57.

I.R. (Nujol): 3250, 1780, 1720, 1680, 1640, 1620 cm^{-1}.

N.M.R. δ ppm (DMSO-d_6): 1.27—1.50 (12H, m), 3.78 (2H, m), 4.65 (1H, q, J=7.0Hz), 5.18—5.86 (3H, m), 5.93 (1H, dd, J=5.0Hz, 8.0Hz;, 6.80 (1H, s), 6.96 (1H, s), 7.07—7.67 (10H, m),
9.44 (d, J=8.0Hz) } (1H)
9.54 (d, J=8 OHz) }

Example 110

Benzhydryl 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - ethoxycarbonylmethoxyimino)acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (5.45 g) was obtained by reacting benzhydryl 7 - [2 - (2 - formamidothiazol - 4 - yl) - 2 - ethoxycarbonylmethoxyimino)acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (6.2 g) with conc. hydrochloric acid (3.8 ml) according to a similar manner to that of Example 57.

I.R. (Nujol): 3250, 1780, 1720, 1662, 1620, 1535 cm^{-1}.

N.M.R. δ ppm (DMSO-d_6): 1.2 (3H, t, J=7Hz), 3.68 (2H, m), 4.15 (2H, q, J=7Hz), 5.28 (1H, d, J=11Hz), 5.65 (1H, d, J=17Hz),5.95 (1H, dd, J=5Hz, 8Hz), 6.82 (1H, dd, J=11Hz, 17Hz), 6.87 (1H, s), 7.00 (1H, s), 7.30—7.70 (10H, m), 9.65 (1H, d, J=8Hz).

Example 111

7 - [2 - (2 - Aminothiazol - 4 - yl) - 2 - tert - butoxycarbonylmethoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer) (1.7 g) was obtained by reacting 7 - [2 - (2 - formamidothiazol - 4 - yl) - 2 - tert - butoxycarbonylmethoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer) (2.1 g) with conc. hydrochloric acid (1.2 ml) according to a similar manner to that of Example 57.

I.R. (Nujol): 3300, 1770, 1725, 1680, 1610, 1550 cm^{-1}.

N.M.R. δ ppm (DMSO-d_6): 1.45 (9H, s), 3.72 (2H, q, J=18Hz), 4.58 (2H, s), 5.22 (1H, d, J=5Hz), 5.33 (1H, d, J=12Hz), 5.58 (1H, d, J=18Hz), 5.82 (1H, dd, J=5Hz, 8Hz), 6.82 (1H, s), 6.98 (1H, dd, J=12Hz, 18Hz), 9.52 (1H, d, JHz).

Example 112

To a mixture of benzhydryl 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - (1 - tert - butoxycarbonyl - 1 - methylethoxyimino)acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (3.9 g) and anisole (3.9 ml) was added trifluoroacetic acid (15.6 ml) under ice-cooling, and the mixture was stirred at ambient temperature for an hour. To the reaction mixture was added diisopropyl ether and the precipitated crystals were collected by filtration and then washed with diisopropyl ether. To the crystals were added ethyl acetate and water, followed by adjusting to pH 7.5 with sodium bicarbonate. The separated aqueous solution was washed with ethyl acetate and then adjusted to pH 2.5 with 10% hydrochloric acid. The precipitated crystals were collected by filtration, washed with water and then dried to obtain 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - (1 - carboxy - 1 - methylethoxyimino)acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer) (1.09 g), mp 173—177°C (dec.). The filtrate and the washings were combined and saturated with sodium chloride, followed by extraction with tetrahydrofuran. The extract was washed with a saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate and then evaporated to dryness to give a residue, which was pulverized with diisopropyl ether and collected by filtration to recover the same object compound (0.59 g). Total yield: 1.68 g.

I.R. (Nujol): 3300, 3200, 1770, 1670, 1640 cm^{-1}.

N.M.R. δ ppm (DMSO-d_6): 1.49 (6H, s), 3.76 (2H, q, J=18.0Hz), 5.24 (1H, d, J=4.0Hz), 5.18—6.98 (3H, m), 6.79 (1H, s), 6.95 (1H, dd, J=12.0Hz, 18.0Hz), 9.41 (1H, d, J=8.0Hz).

Example 113

7 - [2 - (2 - Aminothiazol - 4 - yl) - 2 - (1 - carboxyethoxyimino)acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer) (0.73 g) was obtained by reacting benzhydryl 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - (2 - tert - butoxycarbonylethoxyimino)acetamido] - 3 - viny - 3 - cephem - 4 - carboxylate (syn isomer) (4.7 g) with trifluoroacetic acid (18.8 ml) in the presence of anisole (4.7 ml) according to a similar manner to that of Example 112.

I.R. (Nujol): 3260, 3160, 1770, 1670 cm^{-1}.

N.M.R. δ ppm (DMSO-d_6): 1.44 (3H, d, J=7.0Hz), 3.73 (2H, m), 4.66 (1H, q, J=7.0Hz), 5.23 (1H, d, J=5.0Hz), 5.33 (1H, d, J=11.5Hz), 5.63—6.00 (2H, m), 6.81 (1H, s), 6.97 (1H, dd, J=11.5Hz, 18.0Hz),
9.44 (d, J=8.0Hz) } (1H)
9.49 (d, J=8.0Hz) }

Example 114

7 - [2 - (2 - Aminothiazol - 4 - yl) - 2 - ethoxycarbonylmethoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer) (3.2 g) was obtained by reacting benzhydryl 7 - [2 - (2 - aminothazol - 4 - yl) - 2 - ethoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer)

(5.2 g) with trifluoroacetic acid (12.8 g) in the presence of anisole (3.4 g) according to a similar manner to that of Example 67.

I.R. (Nujol): 3250, 1770, 1670, 1530 cm^{-1}.

N.M.R. δ ppm (DMSO-d_6): 1.22 (3H, t, J=7Hz), 3.70 (2H, broad s), 4.17 (2H, q, J=7Hz), 4.75 (2H, s), 5.23 (1H, d, J=5Hz), 5.35 (1H, d, J=11Hz), 5.58 (1H, d, J=17Hz), 5.82 (1H, dd, J=5Hz, 8Hz), 6.88 (1H, s), 6.98 (1H, dd, J=11Hz, 17Hz), 9.63 (1H, d, J=8Hz).

Example 115

Benzhydryl 7-amino-3-amino-3-vinyl-3-cephem-4-carboxylate hydrochloride (2.3 g) was dissolved in dried ethyl acetate (50 ml) and trimethylsilylacetamide (4.9 g) at 40°C.

On the other hand, to a Vilsmeier reagent, which was prepared by reacting dried N,N-dimethylformamide (0.5 g) with phosphorus oxychloride (1.1 g) is dried ethyl acetate (2.0 ml) in a conventional manner, were added dried tetrahydrofuran (20 ml) and 2-(3-tertbutoxycarbonylpropoxyimino)-2-(2-formamidothiazol-4-yl)acetic acid (syn isomer) (2.1 g), followed by stirring at −3 to 3°C for a while to prepare the activated acid solution.

This solution was added to the ethyl acetate solution obtained before at −10°C with stirring, and the stirring was continued at −10 to −5°C for half an hour. To the reaction mixture was added water, and the separated organic layer was washed with a saturated aqueous sodium bicarbonate and a saturated aqueous sodium chloride, followed by drying over magnesium sulfate. Removal of the solvent gave a residue, which was pulverized with diisopropyl ether to obtain benzhydryl 7 - [2 - (3 - tert - butoxycarbonylpropoxyimino) - 2 - (2 - formamidothiazol - 4 - yl)acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (3.63 g).

I.R. (Nujol): 3280, 3150, 1780, 1720, 1660 cm^{-1}.

N.M.R. δ ppm (DMSO-d_6): 1.43 (9H, s), 1.97 (2H, m), 2.38 (2H, t, J=6.0Hz), 3.79 (2H, q, J=18.0Hz), 4.18 (2H, t, J=6.0Hz), 5.33 (1H, d, J=11.0Hz), 5.34 (1H, d, J=5.0Hz), 5.67 (1H, d, J=17.0Hz), 5.97 (1H, dd, J=5.0Hz, 8.0Hz), 6.82 (1H, dd, J=11.0Hz, 17.0Hz), 7.00 (1H, s), 7.19—7.73 (11H, m), 8.57 (1H, s), 9.77 (1H, d, J=8.0Hz).

Example 116

Benzhydryl 7-amino-3-vinyl-3-cephem-4-carboxylate hydrochloride (10.6 g) was dissolved in methylene chloride (100 ml) and trimethylsilylacetamide (20.6 g) at 25°C.

On the other hand, to a suspension of 2-(5-amino-1,2,4-thiadiazol-3-yl)-2-methoxyiminoacetic acid (syn isomer) (4.0 g) in methylene chloride (100 ml) was added phosphorus oxychloride (12.1 g), followed by stirring at ambient temperature for 1.5 hours. Thereto was added N,N-dimethylformamide (8 ml) at −12 to −10°C and the mixture was stirred at −10 to −8°C for 45 minutes to prepare the activated acid solution.

The activated acid solution was added to the methylene chloride solution obtained before at −30°C with stirring, and the stirring was continued at −15°C for 45 minutes. The reaction mixture was poured into a saturated aqueous sodium bicarbonate (300 ml), followed by stirring for half an hour. During the stirring, the reaction mixture was adjusted to pH 7.5 with sodium bicarbonate. Thereto was added ethyl acetate (500 ml), and the insoluble substance was removed by filtration. The separated organic layer was washed with an aqueous sodium chloride and then dried over magnesium sulfate. Removal of the solvent gave a residue, which was pulverized with diethyl ether to obtain benzhydryl 7 - [2 - (5 - amino - 1,2,4 - thiadiazol - 3 - yl) - 2 - methoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (6.3 g).

I.R. (Nujol): 3300, 3175, 1770, 1720, 1670, 1610, 1510 cm^{-1}.

N.M.R. δ ppm (DMSO-d_6): 3.77 (2H, m), 3.93 (3H, s), 5.25 (1H, d, J=5Hz), 5.27 (1H, d, J=11Hz), 5.62 (1H, d, J=17Hz), 5.92 (1H, dd, J=5Hz, 8Hz), 6.77 (1H, dd, J=11Hz, 17Hz), 6.97 (1H, s), 7.38 (10H, m), 9.62 (1H, d, J=8Hz).

Example 117

Benzhydryl 7 - [2 - (trans - 3 - tert - butoxycarbonylallyloxyimino - 2 - (2 - formamidothiazol - 4 - yl)acetamido) - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (4.83 g) was obtained by reacting benzhydryl 7-amino-3-vinyl-3-cephem-4-carboxylate hydrochloride (3.0 g) with 2-(trans-3-tert-butoxycarbonylallyloxyimino)-2-(2-formamidothiazol-4-yl)acetic acid (syn isomer) (2.7 g) according to similar manners to those of Examples 115 and 116.

I.R. (Nujol): 3250, 1780, 1710, 1660 cm^{-1}.

N.M.R. δ ppm (DMSO-d_6): 1.47 (9H, s), 3.79 (2H, q, J=18.0Hz), 4.89 (2H, m), 5.34 (1h, d, J=11.0Hz), 5.35 (1H, d, J=5.0Hz), 5.68 (1H, d, J=18.0Hz), 5.86—6.30 (2H, m), 6.52—7.22 (2H, m), 7.00 (1H, s), 7.21—7.74 (11H, m), 8.58 (1H, s), 9.91 (1H, d, J=8.0Hz), 12.73 (1H, broad s).

Example 118

Benzhydryl 7 - [2 - cyanomethoxyimino - 2 - (2 - formamidothiazol - 4 - yl)acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (3.1 g) was obtained by reacting benzhydryl 7-amino-3-vinyl-3-cephem-4-carboxylate hydrochloride (2.5 g) with 2-cyanomethoxyimino-2-(2-formamidothiazol-4-yl)acetic acid (syn isomer) (1.6 g) according to similar manners to those of Examples 115 and 116.

I.R. (Nujol): 3180, 1770, 1720, 1680 cm^{-1}.

N.M.R. δ ppm (DMSO-d_6): 3.77 (2H, m), 5.03—6.10 (5H, m), 5.81 (1H, dd, J=5.0Hz, 8.0Hz), 6.43—7.13 (1H, m), 6.96 (1H, s), 7.35 (10H, s), 7.56 (1H, s), 8.53 (1H, s), 9.93 (1H, d, J=8.0Hz).

Example 119

Benzhydryl 7 - [2 - tert - butoxycarbonylmethoxyimino - 2 - (5 - chloro - 2 - formamidothiazol - 4 - yl)acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (5.6 g) was obtained by reacting benzhydryl 7-amino-3-vinyl-3-cephyem-4-carboxylate hydrochloride (3.43 g) with 2-tert-butoxycarbonylmethoxyimino-2-(5-chloro-2-formamidothiazol-4-yl)acetic acid (syn isomer) (3.2 g) according to similar manners to those of Examples 115 and 116.

I.R. (Nujol): 3200, 1780, 1720, 1680, 1606, 1540 cm^{-1}.

N.M.R. δ ppm (DMSO-d_6): 1.43 (9H, s), 3.77 (2H, m), 4.67 (2H, s), 5.30 (1H, d, J=5Hz), 5.32 (1H, d, J=11Hz), 5.65 (1H, d, J=18Hz), 6.03 (1H, dd, J=5Hz, 8Hz), 6.83 (1H, dd, J=11Hz, 18Hz), 7.02 (1H, s), 7.23—7.8 (10H, m), 8.60 (1H, s), 9.73 (1H, d, J=8Hz).

The following compounds were obtained by reacting 7-amino-3-vinylcephalosporanic acid derivatives with the corresponding acylating agents according to similar manners to those of Example 115 and 116.

Example 120

Benzhydryl 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - (3 - tert - butoxycarbonylpropoxyimino)-acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer).

I.R. (Nujol): 3340, 3250, 1780, 1720, 1680, 1620 cm^{-1}.

Example 121

Benzhydryl 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - (trans - 3 - tert - butoxycarbonylpropoxyimino)-acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer).

I.R. (Nujol): 3250, 1770, 1700 1670, 1610 cm^{-1}.

Example 122

Benzhydryl 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - cyanomethoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer).

I.R. (Nujol): 3430, 3250, 1780, 1720, 1680, 1660 cm^{-1}.

Example 123

Benzhydryl 7 - [2 - (2 - amino - 5 - chlorothiazol - 4 - yl) - 2 - tert - butoxycarbonylmethoxyimino-acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer).

I.R. (Nujol): 3425, 3270, 1780, 1720, 1675, 1620, 1540 cm^{-1}.

Example 124

7 - [2 - (5 - Amino - 1,2,4 - thiadiazol - 3 - yl) - 2 - methoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer).

I.R. (Nujol): 3350, 3250, 1770, 1670, 1620, 1530 cm^{-1}.

Example 125

7 - [2 - (2 - Aminothiazol - 4 - yl) - 2 - cyanomethoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer).

I.R. (Nujol): 3330, 2020, 1770, 1670, 1620 cm^{-1}.

Example 126

Pivaloyloxymethyl 7 - [2 - (5 - amino - 1,2,4 - thiadiazol - 3 - yl) - 2 - methoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer).

I.R. (Nujol): 3400—3100, 1770, 1760, 1680, 1620, 1530 cm^{-1}.

Example 127

Phosphorus oxychloride (4.1 g) was added to a suspension of 2-(5-amino-1,2,3-thiadiazol-3-yl)-2-tert-butoxycarbonylmethoxyiminoacetic acid (syn isomer) (2.0 g) in methylene chloride (26 ml), and the mixture was stirred at ambient temperature for 1.5 hours. Thereto was added N,N-dimethylformamide (4.0 ml) at −15°C, followed by stirring at −15 to −5°C for 40 minutes to prepare the activated acid solution.

On the other hand, trimethylsilylacetamide (5.5 g) was added to a suspension of benzhydryl 7-amino-3-vinyl-3-cephem-4-carboxylate hydrochloride (2.6 g) in methylene chloride (26 ml), and the mixture was stirred at 35 to 40°C for 10 minutes.

To this solution was added at a time the activated acid solution prepared before at −10°C, and the mixture was stirred at −10 to −5°C for half an hour. To the reaction mixture was added a saturated aqueous sodium chloride (150 ml) and ethyl acetate (150 ml), followed by adjusting to pH 7.5 with a saturated aqueous sodium bicarbonate. The separated organic layer was washed with a saturated aqueous sodium chloride and then dried over magnesium sulfate. Removal of the solvent gave benzhydryl 7 - [2 - [5 - {N - (N,N - dimethylaminomethylene)amino} - 1,2,4 - thiadiazol - 3 - yl] - 2 - tert - butoxycarbonylmethoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (4.13 g).

I.R. (Nujol): 1770, 1710, 1620 cm^{-1}.

N.M.R. δ ppm (DMSO-d_6): 1.47 (9H, s), 3.09 (3H, s), 3.20 (3H, s), 3.82 (2H, m), 4.71 (2H, s), 5.17—6.17 (3H, m), 5.32 (1H, d, J=5.0Hz), 6.80 (1H, dd, J=12.0Hz, 18.0Hz), 7.00 (1H, s), 7.43 (10H, s), 8.50 (1H, s), 9.69 (1H, d, J=8.0Hz).

Example 128

To a solution of benzhydryl 7 - [2 - tert - butoxycarbonylmethoxyimino - 2 - (2 - formamidothiazol - 4 - yl)acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (2.5 g) in anisole (2.5 ml) and methylene chloride (5.0 ml) was added trifluoroacetic acid (10.0 ml) under ice-cooling, and the mixture was stirred at ambient temperature for 2 hours. To the reaction mixture was added dropwise diisopropyl ether, and the precipitated crystals were collected by filtration, washed with diisopropyl ether to obtain 7 - [2 - carboxymethoxyimino - 2 - (2 - formamidothiazol - 4 - yl)acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer) (1.57 g).

I.R. (Nujol): 3130, 1770, 1670 cm^{-1}.

N.M.R. δ ppm (DMSO-d_6): 3.71 (2H, q, J=18.0Hz), 4.66 (2H, s), 5.22 (1H, d, J=4.0Hz), 5.22—5.85 (2H, m), 5.84 (1H, dd, J=4.0Hz, 8.0Hz), 6.93 (1H, dd, J=12.0 Hz, 18.0Hz), 7.44 (1H, s), 8.50 (1H, s), 9.59 (1h, d, J=8.0Hz), 12.30 (1H, broad s).

Example 129

To a solution of benzhydryl 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - (trans - 3 - tert - butoxycarbonylallyloxyimino) - acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (4.4 g) and anisole (4.4 ml) in methylene chloride (9.0 ml) was added trifluoroacetic acid (17.6 ml) under ice-cooling, and the mixture was stirred at ambient temperature for 2 hours. To the reaction mixture was added diisopropyl ether, and the precipitated substance was collected by filtration, which was washed with diisopropyl ether. To this substance were added ethyl acetate and water, and then adjusted to pH 7.5 with a saturated aqueous sodium bicarbonate. The separated aqueous layer was washed with ethyl acetate, and the remaining ethyl acetate in the aqueous solution was completely removed by evaporation, followed by adjusting to pH 2.2 with 10% hydrochloric acid. The precipitated substance was collected by filtration and then dried to obtain 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - (trans - 3 - carboxyallyloxyimino)-acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer) (2.31 g).

I.R. (Nujol): 3250, 1760, 1690, 1650 cm^{-1}.

N.M.R. δ ppm (DMSO-d_6): 3.73 (2H, q, J=16.0Hz), 4.84 (2H, m), 5.24 (1H, d, J=4.0Hz), 5.34 (1H, d, J=12.0Hz), 5.47—6.23 (3H, m) 6.63—7.34 (2H, m), 6.83 (1H, s), 9.77 (1H, d, J=8.0Hz).

Example 130

7 - [2 - (2 - Aminothiazol - 4 - yl) - 2 - (3 - carboxypropoxyimino) - acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer) (1.75 g) was obtained by reacting benzhydryl 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - (3 - tert - butoxycarbonylpropoxyimino) - acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (3.2 g) with trifluoroacetic acid (12.8 ml) in the presence of anisole (3.2 ml) according to similar manners to those of Examples 128 and 129.

I.R. (Nujol): 3300, 1760, 1660 cm^{-1}.

N.M.R. δ ppm (DMSO-d_6): 1.95 (2H, m), 2.37 (2H, t, J=6.0Hz), 3.73 (2H, q, J=17.0Hz), 4.13 (2H, t, J=6.0Hz), 5.23 (1H, d, J=5.0Hz), 5.23—6.00 (3H, m), 6.79 (1H, s), 7.00 (1H, dd, J=11.0Hz, 18.0Hz), 9.65 (1H, d, J=8.0Hz).

Example 131

7 - [2 - (2 - Amino - 5 - chlorothiazol - 4 - yl) - 2 - carboxymethoxyimino - acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer) (2.2 g) was obtained by reacting benzhydryl 7 - [2 - (2 - amino - 5 - chlorothiazol - 4 - yl) - 2 - tert - butoxycarbonylmethoxyimino - acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (4.6 g) with trifluoroacetic acid (14.4 g) in the presence of anisole (2.7 g) according to similar manners to those of Example 128 and 129.

I.R. (Nujol): 3400, 3180, 1770, 1685, 1650, 1610 cm^{-1}.

N.M.R. δ ppm (DMSO-d_6): 3.70 (2H, q, J=18Hz), 4.63 (2H, s), 5.18 (1H, d, J=5Hz), 5.33 (1H, d, J=11Hz), 5.56 (1H, d, J=18Hz), 5.83 (1H, dd, J=5Hz, 8Hz), 6.95 (1H, dd, J=11Hz, 18Hz), 9.45 (1H, d, J=8Hz).

Example 132

Trifluoroacetic acid (16.0 ml) was added to a solution of benzhydryl 7 - [2 - [5 - {N - (N,N - dimethylaminomethylene)amino} - 1,2,4 - thiadiazol - 3 - yl] - 2 - tert - butoxycarbonylmethoxyimino-acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (4.0 g) in methylene chloride (8.0 ml) and anisole (4.0 ml) under ice-cooling, and the mixture was stirred at ambient temperature for 1.5 hours. The reaction mixture was added dropwise to diisopropyl ether (200 ml), and the precipitated substance was collected by filtration and then added to a mixture of water and ethyl acetate, followed by adjusting to pH 7.5 with a saturated aqueous sodium bicarbonate. The separated aqueous layer was saturated with sodium chloride and adjusted to pH 2.5 with 10% hydrochloric acid, followed by extraction with a mixed solvent of ethyl acetate and tetrahydrofuran (1:2 by volume). The extract was washed with a saturated aqueous sodium chloride and then dried over magnesium sulfate. Removal of the solvent gave a residue, which was washed with diethyl ether and collected by filtration to obtain 7 - [2 - (5 - formamido - 1,2,4 - thiadiazol - 3 - yl) - 2 - carboxymethoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer) (1.75 g).

I.R. (Nujol): 3200, 1770, 1670 cm^{-1}.

N.M.R. δ ppm (DMSO-d_6): 3.70 (2H, m), 4.75 (2H, s), 5.24 (1H, d, J=5.0Hz), 5.33 (1H, d, J=12.0Hz), 5.61 (1H, d, J=18.0Hz), 5.91 (1H, dd, J=5.0Hz, 8.0Hz), 6.96 (1H, dd, J=12.0Hz, 18.0Hz), 8.87 (1H, s), 9.70 (1H, d, J=8.0Hz), 13.47 (1H, broad s).

Example 133

To a solution of benzhydryl 7 - [2 - tert - butoxycarbonylmethoxyimino) - 2 - (2 - formamidothiazol - 4 - yl)acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer) (2 g) and anisole (8.0 ml) in dioxane (8 ml) and tert-butyl alcohol (8.0 ml) was added p-toluenesulfonic acid (2.2 g), followed by stirring at 60°C for 5 hours. To the reaction mixture was added ethyl acetate and water, and then adjusted to pH 7.5 with a saturated aqeuous sodium bicarbonate. The aqueous layer was separated and washed with ethyl acetate, and thereto were added ethyl acetate and tetrahydrofuran, followed by adjusting to pH 2.2 with 10% hydrochloric acid. After the aqueous layer was saturated with sodium chloride, the organic layer was separated with sodium chloride, the organic layer was separated, washed with a saturated aqueous sodium chloride and the dried over magnesium sulfate. Removal of the solvent gave a residue, which was pulverized with diisopropyl ether and collected by filtration. To this substance was added water and then adjusted to pH 5.5 with 2N aqueous sodium hydroxide. The aqueous solution was subjected to column chromatography on a nonionic adsorption resin, "Diaion HP—20" (20 ml), and elution was carried out with water (40 ml). To the eluate were added ethyl acetate and tetrahydrofuran, followed by adjusting to pH 2.2 with 10% hydrochloric acid. After the aqueous layer was saturated with sodium chloride, the organic layer was separated, washed with a saturated aqueous sodium chloride and then dried over magnesium sulfate. Removal of the solvent gave a residue, which was pulverized with diisopropyl ether and collected by filtration to obtain 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - carboxymethoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer) (0.31 g).

I.R. (Nujol): 3350, 1770, 1680, 1640 cm^{-1}.

N.M.R. δ ppm (DMSO-d_6): 3.70 (2H, q, J=18Hz), 4.62 (2H, s), 5.21 (1H, d, J=5Hz), 5.82 (1H, dd, J=5Hz, 8Hz), 5—6 (2H, m), 6.82 (1H, s), 7.22 (2H, broad s), 6.5—7.5 (1H, m), 9.5 (1H, d, J=8Hz).

The following compounds were obtained by reacting 7-acylamino-3-vinylcephalosporanic acid derivatives having a formamido group, a tert-butoxycarbonyl group and a benzhydryl ester with p-toluenesulfonic acid in the presence of anisole according to a similar manner to that of Example 133.

Example 134

7 - [2 - (2 - Aminothiazol - 4 - yl) - 2 - (trans - 3 - carboxyallyloxyimino)acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer).

I.R. (Nujol): 3250, 1760, 1690, 1650 cm^{-1}.

Example 135

7 - [2 - (2 - Aminothiazol - 4 - yl) - 2 - (3 - carboxypropoxyimino)acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer).

I.R. (Nujol): 3300, 1760, 1660 cm^{-1}.

Example 136

7 - [2 - (2 - Amino - 5 - chlorothiazol - 4 - yl) - 2 - carboxymethoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer).

I.R. (Nujol): 3400, 3180, 1770, 1685, 1650, 1610 cm^{-1}.

Example 137

A mixture of benzhydryl 7 - [2 - (3 - tert - butoxycarbonylpropoxyimino) - 2 - (2 - formamidothiazol - 4 - yl)acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (3.5 g), conc. hydrochloric acid (1.0 g), methanol (30 ml) and tetrahydrofuran (15.0 ml) was stirred at ambient temperature for 2.5 hours. To the reaction mixture was added ethyl acetate, followed by adjusting to pH 7.5 with a saturated aqueous sodium bicarbonate. The separated organic layer was washed with a saturated aqueous sodium chloride and then dried over magnesium sulfate. Removal of the solvent gave a residue, which was pulverized with diisopropyl ether to obtain benzhydryl 7 - [2 - (3 - tert - butoxycarbonylpropoxyimino) - 2 - (2 - aminothiazol - 3 - yl)acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer) (3.33 g).

I.R. (Nujol): 3340, 3250, 1780, 1720, 1680, 1620 cm^{-1}.

N.M.R. δ ppm (DMSO-d_6): 1.40 (9H, s), 1.87 (2H, m), 2.35 (2H, t, J=7.0Hz), 3.76 (2H, m), 4.11 (2H, t, J=7.0Hz), 5.30 (1H, d, J=5.0Hz), 5.32 (1H, d, J=12.0Hz), 5.66 (1H, d, J=18.0Hz), 5.91 (1H, dd, J=5.0Hz, 8.0Hz), 6.78 (1H, s), 6.79 (1H, dd, J=12.0Hz, 18.0Hz), 6.98 (1H, s), 7.39 (10H, s), 9.66 (1H, d, J=8.0Hz).

Example 138

A mixture of benzhydryl 7 - [2 - (trans - 3 - tert - butoxycarbonylallyloxyimino) - 2 - (2 - formamidothiazol - 4 - yl)acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (4.7 g), conc. hydrochloric acid (1.34 g), methanol (30 ml) and tetrahydrofuran (10 ml) was stirred at ambient temperature for 2.5 hours. To the reaction mixture was added ethyl acetate, followed by adjusting to pH 7.5 with a saturated aqueous sodium bicarbonate. The separated organic layer was washed with a saturated aqueous sodium chloride and then dried over magnesium sulfate. Removal of the solvent gave a residue, which was pulverized with diisopropyl ether to obtain benzhydryl 7 - [2 - (trans - 3 - tert -

butoxycarbonylallyloxyimino) - 2 - (2 - aminothiazol - 4 - yl)acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (4.50 g).

I.R. (Nujol): 3250, 1770, 1700, 1670, 1610 cm^{-1}.

N.M.R. δ ppm (DMSO-d_6): 1.45 (9H, s), 3.76 (2H, m), 4.86 (2H, m), 5.34 (1H, d, J=12.0Hz), 5.35 (1H, d, J=5.0Hz), 5.68 (1H, d, J=18.0Hz), 5.77—6.30 (2H, m), 6.54—7.17 (2H, m), 6.86 (1H, s), 7.00 (1H, s), 7.17—7.70 (10H, m), 9.81 (1H, d, J=8.0Hz).

Example 139

Benzhydryl 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - cyanomethoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (2.17 g) was obtained by reacting benzhydryl 7 - [2 - (2 - formamidothiazol - 4 - yl) - 2 - cyanomethoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (3.0 g) with conc. hydrochloric acid (0.35 g) according to similar manners to those of Examples 137 and 138.

I.R. (Nujol): 3430, 3250, 1780, 1720, 1680, 1660 cm^{-1}.

N.M.R. δppm (DMSO-d_6): 3.77 (2H, m), 5.02 (2H, s), 5.10—6.08 (2H, m), 5.28 (1H, d, J=5.0Hz), 5.85 (1H, dd, J=5.0Hz, 8.0Hz), 6.83 (1H, dd, J=10.0Hz, 18.0Hz), 6.89 (1H, s), 6.95 (1H, s), 7.09—7.63 (10H, m), 9.83 (1H, d, J=8.0Hz).

Example 140

Benzhydryl 7 - [2 - (2 - amino - 5 - chlorothiazol - 4 - yl) - 2 - tert - butoxycarbonylmethoxyimino-acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (4.6 g) was obtained by reacting benzhydryl 7 - [2 - (2 - formamido - 5 - chlorothiazol - 4 - yl) - 2 - tert - butoxycarbonylmethoxyimino-acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (5.5 g) with conc. hydrochloric acid (2.3 ml) according to similar manners to those of Examples 137 and 138.

I.R. (Nujol): 3425, 3270, 1780, 1720, 1675, 1620, 1540 cm^{-1}.

N.M.R. δppm (DMSO-d_6): 1.43 (9H, s), 3.77 (2H, m), 4.63 (2H, s), 5.30 (1H, d, J=5Hz), 5.32 (1H, d, J=11Hz), 5.68 (1H, d, J=17Hz), 6.00 (1H, dd, J=5Hz, 8Hz), 6.85 (1H, dd, J=11Hz, 17Hz), 7.03 (1H, s), 7.22—7.90 (10H, m), 9.60 (1H, d, J=8Hz).

The following compounds were obtained by reacting 7-acylamino-3-vinylcephalosporanic acid derivatives having a formamido group with conc. hydrochloric acid according to similar manners to those of Examples 137 and 138.

Example 141

Benzhydryl 7 - [2 - (5 - amino - 1,2,4 - thiadiazol - 3 - yl) - 2 - methoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer).

I.R. (Nujol): 3300, 3175, 1770, 1720, 1670, 1610, 1510 cm^{-1}.

Example 142

7 - [2 - (5 - Amino - 1,2,4 - thiadiazol - 3 - yl) - 2 - methoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer).

I.R. (Nujol): 3350, 3250, 1770, 1670, 1620, 1530 cm^{-1}.

Example 143

7 - [2 - (2 - Aminothiazol - 4 - yl) - 2 - cyanomethoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer).

I.R. (Nujol): 3330, 2020, 1770, 1670, 1620 cm^{-1}.

Example 144

7 - [2 - (2 - Aminothiazol - 4 - yl) - 2 - (trans - 3 - carboxyallyloxyimino)acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer).

I.R. (Nujol): 3250, 1760, 1690, 1650 cm^{-1}.

Example 145

7 - [2 - (2 - Aminothiazol - 4 - yl) - 2 - (3 - carboxypropoxyimino)acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer).

I.R. (Nujol): 3300, 1760, 1660 cm^{-1}.

Example 146

7 - [2 - (2 - Amino - 5 - chlorothiazol - 4 - yl) - 2 - carboxymethoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer).

I.R. (Nujol): 3400, 3180, 1770, 1685, 1650, 1610 cm^{-1}.

Example 147

Pivaloyloxymethyl 7 - [(2 - (5 - Amino - 1,2,4 - thiadiazol - 3 - yl) - 2 - methoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer).

I.R. (Nujol): 3400—3100, 1770, 1760, 1680, 1620, 1530 cm^{-1}.

Example 148

To a suspension of benzhydryl 7 - [2 - (5 - amino - 1,2,4 - thiadiazol - 3 - yl) - 2 - methoxyimino-acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (6.2 g) in methylene chloride (60 ml) were added anisole (9.3 g) and trifluoroacetic acid (24.5 g), and the mixture was stirred at ambient temperature for 1.5 hours. After removal of the solvent, the residue was added dropwise to diisopropyl ether (600 ml), and the precipitated substance was collected by filtration. This substance was suspended in water (50 ml) and then adjusted to pH 7.5 with 2N aqueous sodium hydroxide, followed by washing twice with a mixture of ethyl acetate (50 ml) and tetrahydrofuran (50 ml). To the resultant aqueous solution were added ethyl acetate (50 ml) and tetrahydrofuran (50 ml), and the mixture was saturated with sodium chloride and adjusted to pH 1.0 with 10% hydrochloric acid. The organic layer was separated, and the remaining aqueous solution was extracted twice with a mixture of ethyl acetate and tetrahydrofuran. The combined organic solution was washed with an aqueous sodium chloride and then dried over magnesium sulfate. Removal of the solvent gave a residue, which was pulverized with diethyl ether to obtain 7 - [2 - (5 - amino - 1,2,4 - thiadiazol - 3 - yl) - 2 - methoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer) (3.9 g).

I.R. (Nujol): 3350, 3250, 1770, 1670, 1620, 1530 cm^{-1}.

N.M.R. δppm (DMSO-d_6): 3.71 (2H, m), 3.93 (3H, s), 5.18 (1H, d, J=5Hz), 5.32 (1H, d, J=11Hz), 5.55 (1H, d, J=17Hz), 5.82 (1H, dd, J=5Hz, 8Hz), 6.95 (1H, dd, J=11Hz, 17Hz), 9.58 (1H, d, J=8Hz).

Example 149

7 - [2 - (2 - Aminothiazol - 4 - yl) - 2 - cyanomethoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer) (0.92 g) was obtained by reacting benzhydryl 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - cyanomethoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (2.1 g) with trifluoroacetic acid (8.4 ml) in the presence of anisole (2.1 ml) according to a similar manner to that of Example 148.

I.R. (Nujol): 3330, 2020, 1770, 1670, 1620 cm^{-1}.

N.M.R. δppm (DMSO-d_6): 3.73 (2H, q, J=18.0Hz), 5.02 (2H, s), 5.23 (1H, d, J=5.0Hz), 5.34 (1H, d, J=12.0Hz), 5.37—6.80 (1H, m), 5.79 (1H, dd, J=5.0Hz, 8.0Hz), 6.63—7.38 (1H, m), 6.91 (1H, s), 9.83 (1H, d, J=8.0Hz).

Example 150

To a suspension of 7 - [2 - methoxyimino - 2 - (5 - amino - 1,2,4 - thiadiazol - 3 - yl)acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer) (2.3 g) in water (30 ml) was added sodium bicarbonate (0.47 g), and the mixture was stirred for a while. The insoluble substance was removed by filtration, and then the filtrate was lyophilized to prepare sodium salt of the above compound (2.0 g).

This product was dissolved in N,N-dimethylformamide (20 ml), and thereto was added dropwise a solution of iodomethyl pivalate (1.23 g) in N,N-dimethylformamide (3 ml) under ice-cooling, followed by stirring below 5°C for 10 minutes. To the reaction mixture were added ethyl acetate (50 ml) and water (50 ml), and the organic layer was separated, and washed three times with a saturated aqueous sodium bicarbonate (30 ml) and three times with an aqueous sodium chloride (30 ml), followed by drying over magnesium sulfate. Removal of the solvent gave a residue, which was pulverized with diisopropyl ether to obtain pivaloyloxymethyl 7 - [2 - methoxyimino - 2 - (5 - amino - 1,2,4 - thiadiazol - 3 - yl)acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (1.4 g), mp 125—133°C (dec.).

I.R. (Nujol): 3400—3100, 1770, 1760, 1680, 1620, 1530 cm^{-1}.

N.M.R. δppm (DMSO-d_6): 1.15 (9H, s), 3.77 (2H, q, J=17Hz), 3.93 (3H, s), 5.23 (1H, d, J=5Hz), 5.38 (1H, d, J=11Hz), 5.7 (1H, d, J=17Hz), 5.7—6.1 (3H, m), 6.85 (1H, dd, J=11Hz, 17Hz), 8.15 (2H, broad s), 9.67 (1H, d, J=8Hz).

Example 151

2 - (5 - Amino - 1,2,4 - thiadiazol - 3; - l) - 2 - tert - butoxycarbonylmethoxyimino)acetic acid (syn isomer) (2.5 g) was added to a solution of phosphorus pentachloride (1.7 g) in methylene chloride at −18°C, followed by stirring at −5 to −15°C for an hour. After dried diisopropyl ether (75 ml) was added thereto at −10 to −5°C, the mixture was stirred at ambient temperature for 10 minutes. The precipitates were collected by filtration and then washed with diisopropyl ether.

On the other hand, trimethylsilylacetamide (5.8 g) was added to a suspension of benzhydryl 7 - amino - 3 - vinyl - 3 - cephem - 4 - carboxylate hydrochloride (2.7 g) in methylene chloride (27 ml), followed by stirring for a while. To this solution was added the precipitates obtained above at −10°C, and the mixture was stirred at the same temperature for half an hour. To the reaction mixture were added water (80 ml) and ethyl acetate (200 ml), followed by separation of the organic layer. Thereto was added water, and the mixture was adjusted to pH 7.5 with a saturated aqueous sodium bicarbonate. The separated organic layer was washed with a saturated aqueous sodium chloride and then dried over magnesium sulfate. Removal of the solvent gave benzhydryl 7 - [2 - (5 - amino - 1,2,4 - thiadiazol - 3 - yl) - 2 - tert - butoxycarbonylmethoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (3.53 g).

I.R. (Nujol): 3400, 1770, 1720, 1670, 1620 cm^{-1}.

N.M.R. δppm (DMSO-d_6): 1.46 (9H, s), 3.77 (2H, q, J=19.0Hz), 4.67 (2H, s), 5.30 (1H, d, J=5.0Hz), 5.33 (1H, d, J=11.0Hz), 5.66 (1H, d, J=17.0Hz), 5.96 (1H, dd, J=5.0Hz, 9.0Hz), 6.80 (1H, dd, J=11.0Hz, 17.0Hz), 6.99 (1H, s), 7.43 (10H, s), 8.23 (2H, broad s), 9.63 (1H, d, J=9.0Hz).

Example 152

Benzhydryl 7 - [2 - (O,O - diethylphosphonomethoxyimino) - 2 - (2 - formamidothiazol - 4 - yl)-acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (4.3 g), mp 135 to 142°C, was obtained by reacting benzhydryl 7 - amino - 3 - vinyl - 3 - cephem - 4 - carboxylate (4.7 g) with an activated acid solution, which was prepared from 2 - (O,O - diethylphosphonomethoxyimino) - 2 - (2 - formamidothiazol - 4 - yl) - acetic acid (syn isomer) (5.5 g), phosphorus oxychloride (2.07 ml) and N,N-dimethylformamide (1.75 ml) in tetrahydrofuran (55 ml) in a conventional manner, according to similar manners to those of Example 151.

I.R. (Nujol): 3400, 3160, 1785, 1723, 1675 cm^{-1}.

N.M.R. δppm (DMSO-d_6): 1.25 (6H, t, J=6Hz), 3.73 (2H, m), 4.13 (4H, m), 4.57 (2H, d, J=7Hz), 5.28 (1H, d, J=5Hz), 5.2—5.8 (2H, m), 5.90 (1H, m), 6.80 (1H, dd, J=11Hz, 18Hz), 6.95 (1H, s), 7.37 (10H, m), 7.47 (1H, s), 8.53 (1H, s), 9.80 (1H, d, J=8Hz), 12.7 (1H, broad s).

Example 153

Trifluoroacetic acid (13.6 ml) was added to a solution of benzhydryl 7 - [2 - (5 - amino - 1,2,4 - thiadiazol - 3 - yl) - 2 - tert - butoxycarbonylmethoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (3.4 g) in methylene chloride (7.0 ml) and anisole (3.4 ml) under ice-cooling, followed by stirring at ambient temperature for 1.5 hours. The reaction mixture was added dropwise to diisopropyl ether (150 ml), and the precipitates were collected by filtration and then added to a mixture of water and ethyl acetate. After adjusting to pH 7.5 with a saturated aqueous sodium bicarbonate, the aqueous layer was separated and then adjusted to pH 2.0 with 10% hydrochloric acid. The precipitates were collected by filtration, washed with cold water and then dried to obtain 7 - [2 - (5 - amino - 1,2,4 - thiadiazol - 3 - yl) - 2 - carboxymethoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer) (1.39 g).

I.R. (Nujol): 3380, 3280, 1760, 1720, 1670 cm^{-1}.

N.M.R. δppm (DMSO-d_6): 3.73 (2H, q, J=18.5Hz), 4.69 (2H, s), 5.21 (1H, d, J=5.0Hz), 5.33 (1H, d, J=12.0Hz), 5.60 (1H, d, J=18.0Hz), 5.86 (1H, dd, J=5.0Hz, 8.0Hz), 6.98 (1H, dd, J=12.0Hz, 18.0Hz), 8.16 (2H, broad s), 9.56 (1H, d, J=18.0Hz).

Example 154

To a solution of benzhydryl 7 - [2 - (O,O - diethylphosphonomethoxyimino) - 2 - (2 - formamidothiazol - 4 - yl)acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (4.2 g) in methylene chloride (20 ml) and anisole (2 ml) was added trifluoroacetic acid (5 ml) under ice-cooling, followed by stirring at 10°C for 1.5 hours. The reaction mixture was added dropwise to diisopropyl ether (400 ml), and the precipitates were collected by filtration and washed with diisopropyl ether, followed by drying under reduced pressure to obtain 7 - [2 - (O,O - diethylphosphonomethoxyimino) - 2 - (2 - formamidothiazol - 4 - yl)acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer) (2.8 g), mp 173 to 176°C.

I.R. (Nujol): 3160, 1775 (broad), 1680 (broad) cm^{-1}.

N.M.R. δppm (DMSO-d_6): 1.28 (6H, t, J=6Hz), 3.76 (2H, m), 4.17 (4H, m), 4.58 (2H, d, J=7Hz), 5.23 (1H, d, J=5Hz), 5.36 (1H, d, J=11Hz), 5.63 (1H, d, J=18Hz), 5.87 (1H, dd, J=5Hz, 8Hz), 7.0 (1H, dd, J=11Hz, 18Hz), 7.70 (1H, s), 8.56 (1H, s), 9.82 (1H, d, J=8Hz), 12.7 (1H, broad s).

Example 155

To a solution of 7 - [2 - (O,O - diethylphosphonomethoxyimino) - 2 - (2 - formamidothiazol - 4 - yl)acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer) (1.725 g) in methylene chloride (26 ml) were added bis(trimethylsilyl)acetamide (3.05 g) and trimethylsilyl iodide (3.0 g) at 25 to 28°C, followed by stirring at ambient temperature for 18 hours. Removal of the solvent gave a residual oil, which was dissolved in methanol (25 ml). After addition of conc. hydrochloric acid (2 ml), the mixture was stirred at 30°C for 2 hours. Removal of the solvent gave a residue, which was dissolved in water (50 ml) and adjusted to pH 5.5 with 1N aqueous sodium hydroxide. This aqueous solution was subjected to column chromatography on a nonionic adsorption resin "Diaion HP—20". After washing with water, elution was carried out with 10% aqueous methanol. The eluates containing a desired compound were collected and then lyophilized to obtain 7 - [2 - phosphonomethoxyimino - 2 - (2 - aminothiazol - 4 - yl)acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer) (1.0 g), mp 185°C (dec.).

I.R. (Nujol): 3300 (broad), 1780, 1658, 1600 cm^{-1}.

N.M.R. δppm (D_2O + $NaHCO_3$): 3.70 (2H, m), 4.32 (2H, d, J=8Hz), 5.28 (1H, d, J=5Hz), 5.43 (1H, d, J=18Hz), 5.50 (1H, d, J=11Hz), 5.83 (1H, d, J=5Hz), 6.93 (1H, dd, J=11Hz, 18Hz), 7.0 (1H, s).

The following compound was obtained by recting 7-acylamino-3-vinylcephalosporanic acid derivatives having a formamido group with conc. hydrochloric acid according to similar manners to those of Examples 137 and 138.

Example 156

7 - [2 - (5 - Amino - 1,2,4 - thiadiazol - 3 - yl) - 2 - carboxymethoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer).

I.R. (Nujol): 3380, 3280, 1760, 1720, 1670 cm^{-1}.

Example 157

To a suspension of benzhydryl 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - methoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (0.9 g) in methylene chloride (10 ml) and anisole (0.66 g) was added trifluoroacetic acid (2.5 g) under ice-cooling, followed by stirring at ambient temperature for an hour. The reaction mixture was added dropwise to diisopropyl ether (100 ml), and the precipitates were collected by filtration and suspended in a mixture of ethyl acetate and water, followed by adjusting to pH 7 with a saturated aqueous sodium bicarbonate. The separated aqueous solution was saturated with sodium chloride, and thereto was added a mixed solvent of ethyl acetate and tetrahydrofuran (8:2 by volume). After adjusting to pH 3.2 with 10% hydrochloric acid, the organic layer was separated out, washed with a saturated aqueous sodium chloride and then dried over magnesium sulfate. Removal of the solvent gave a residue, which was washed with diisopropyl ether to obtain 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - methoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer) (0.4 g).

I.R. (Nujol): 3400—3100, 1780, 1660, 1630, 1540 cm^{-1}.

N.M.R. δppm (DMSO-d_6): 3.72 (2H, q, J=18Hz), 3.87 (3H, s), 5.20 (1H, d, J=5Hz), 5.33 (1H, d, J=11Hz), 5.58 (1H, d, J=18Hz), 5.78 (1H, dd, J=5Hz, 8Hz), 6.77 (1H, s), 6.95 (1H, dd, J=11Hz, 18Hz), 9.62 (1H, d, J=8Hz).

Example 158

Vilsmeier reagent was prepared from phosphorus oxychloride (1.8 g) and N,N-dimethylformamide (0.8 g) in ethyl acetate (3.2 ml) in a conventional manner. 2 - (2 - Cyclopenten - 1 - yloxyimino) - 2 - (2 - formamidothiazol - 4 - yl)acetic acid (syn isomer) (2.7 g) was added to the stirred suspension of Vilsmeier reagent in dry tetrahydrofuran (30 ml) under ice-cooling and stirred for 30 min. at same temperature [Solution A]. Trimethylsilylacetamide (8.1 g) was added to the stirred suspension of 7 - amino - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (2.0 g) in ethyl acetate, and the mixture was stirred for 10 minutes at 35 to 40°C. To the mixture was added the solution A at a time at −10°C and stirred at same temperature for 0.5 hour. Water (40 ml) was added to the reaction mixture, and the separated organic layer was added to water. The mixture was adjusted to pH 7.5 with a saturated aqueous sodium bicarbonate. The separated aqueous layer was adjusted to pH 2.0 with 10% hydrochloric acid and extracted with ethyl acetate. The extract was washed with a saturated aqueous sodium chloride, and dried over magnesium sulfate. The solvent was removed to give precipitates of 7 - [2 - (2 - cyclopenten - 1 - yloxyimino) - 2 - (2 - formamidothiazol - 4 - yl)acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer) (3.20 g).

I.R. (Nujol): 3200, 1780, 1680, 1650 cm^{-1}.

N.M.R. δppm (DMSO-d_6): 1.79—2.78 (4H, m), 3.73 (2H, q, J=20.0Hz), 5.22 (1H, d, J=5.0Hz), 5.33 (1H, d, J=12.0Hz), 5.60 (1H, d, J=18.0Hz), 5.71—6.28 (4H, m), 6.96 (1H, dd, J=12.0Hz, 18.0Hz), 7.40 (1H, s), 8.53 (1H, s), 9.63 (1H, d, J=8.0Hz).

Example 159

A mixture of 7 - [2 - (2 - cyclopenten - 1 - yloxyimino) - 2 - (2 - formamidothiazol - 4 - yl)acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer) (3.1 g) in methanol (22 ml), tetrahydrofuran (10 ml) and conc. hydrochloric acid (1.3 g) was stirred for 2.5 hours at ambient temperature. The reaction mixture was added to a mixture of water and ethyl acetate, and adjusted to pH 7.5 with a saturated aqueous sodium bicarbonate. The separated aqueous layer was adjusted to pH 3.0 with 10% hydrochloric acid. The precipitates were filtered off, washed with water and dried over phosphorus pentoxide in vacuo to give 7 - [2 - (2 - cyclopenten - 1 - yloxyimino) - 2 - (2 - aminothiazol - 4 - yl)acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer) (2.7 g).

I.R. (Nujol): 3270, 1765, 1650 cm^{-1}.

N.M.R. δppm (DMSO-d_6): 1.92—2.75 (4H, m), 3.73 (2H, q, J=18.0Hz), 5.21 (1H, d, J=5.0Hz), 5.21—6.33 (6H, m), 6.80 (1H, s), 6.96 (1H, dd, J=11.0Hz, 18.0Hz), 9.62 (1H, d, J=8.0Hz).

Example 160

Conc. hydrochloric acid (0.18 g) was added to a solution of benzhydryl 7 - [2 - (tert - butoxycarbonyl-methoxyimino) - 2 - (2 - aminothiazol - 4 - yl)acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (3.0 g) in formic acid (12 ml) at 10°C and stirred for 2.5 hours at ambient temperature. The reaction mixture was poured into diisopropyl ether (100 ml). The precipitates were collected by filtration, washed with diisopropyl ether and dried to give 7 - [2 - carboxymethoxyimino - 2 - (2 - aminothiazol - 4 - yl)acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid mono-hydrochloride (syn isomer) (1.6 g).

I.R. (Nujol): 1760, 1670, 1630 cm^{-1}.

N.M.R. δppm (DMSO-d_6): 3.74 (2H, m), 4.75 (2H, s), 5.25 (1H, d, J=5.0Hz), 5.36 (1H, d, J=12.0Hz), 5.61 (1H, d, J=18.0Hz), 5.80 (1H, dd, J=5.0Hz, 8.0Hz), 6.70—7.47 (1H, m), 7.06 (1H, s), 9.78 (1H, d, J=8.0Hz).

This reaction could be carried out by using the following reagents and solvents.

Reagents	Solvents	Yield (%)
conc. hydrochloric acid	acetic acid	30
p-toluenesulfonic acid	formic acid	90
"	acetic acid	50
methanesulfonic acid	formic acid	89
"	acetic acid	65

Example 161

2-Aminooxyacetic acid hemihydrochloride (1.7 g) was added to a solution of 7 - [(2 - aminothiazol - 4 - yl)glyoxylamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (2.0 g) and sodium acetate trihydrate (0.7 g) in water (40 ml), and the mixture was adjusted to pH 5.2 with 10% aqueous sodium hydroxide and then stirred for 3.5 hours at 50°C. During the stirring, the mixture was adjusted to pH 5.0 to 5.4 with the same. The reaction mixture was further adjusted to pH 2.2 with 10% hydrochloric acid under ice-cooling. The precipitates were collected by filtration, washed with water and then dried over phosphorus pentoxide in vacuo to give 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - carboxymethoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer) (1.13 g).

I.R. (Nujol): 3350, 1770, 1680, 1640 cm^{-1}.

The following compounds were obtained by reacting 7-acylaminocephalosporanic acid derivatives having an oxo group with the corresponding O-substituted hydroxylamine according to a similar manner to that of Example 161.

Example 162

7 - [2 - (2 - Aminothiazol - 4 - yl) - 2 - methoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer).

I.R. (Nujol): 3400—3100, 1780, 1660, 1630, 1540 cm^{-1}.

Example 163

Pivaloyloxymethyl 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - methoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer).

I.R. (Nujol): 3400—3100, 1770, 1745, 1670, 1610, 1530 cm^{-1}.

Example 164

Acetoxymethyl 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - methoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer).

I.R. (Nujol): 3300, 1765 (broad), 1660, 1610, 1535 cm^{-1}.

Example 165

Propionyloxymethyl 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - methoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer).

I.R. (Nujol): 3350, 1770 (broad), 1650, 1620, 1530 cm^{-1}.

Example 166

Isobutyryloxymethyl 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - methoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer).

I.R. (Nujol): 3400—3100, 1780—1740, 1670, 1610, 1530 cm^{-1}.

Example 167

1 - Acetoxypropyl 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - methoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer).

I.R. (Nujol): 3300, 1765, 1670, 1610 cm^{-1}.

Example 168

L - 2 - Amino - 2 - carboxyethyl 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - methoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer).

I.R. (Nujol): 3200, 1770, 1735, 1650 (broad) cm^{-1}.

Example 169

Phthalid - 3 - yl 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - methoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer).

I.R. (Nujol): 3300, 1775, 1670, 1610, 1530 cm^{-1}.

Example 170

7 - [2 - (2 - Aminothiazol - 4 - yl) - 2 - allyloxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer).

I.R. (Nujol): 3250, 1770, 1655, 1605, 1545 cm^{-1}.

Example 171

7 - [2 - (2 - Aminothiazol - 4 - yl) - 2 - propargyloxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer).

I.R. (Nujol): 3250, 1760, 1680, 1620, 1530 cm^{-1}.

Example 172

7 - [2 - (2 - Aminothiazol - 4 - yl) - 2 - ethoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer).

I.R. (Nujol): 3300, 1770, 1660, 1545 cm^{-1}.

Example 173

Pivaloyloxymethyl 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - ethoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer).

I.R. (Nujol): 3300, 1780, 1740, 1670, 1610, 1530 cm^{-1}.

Example 174

7 - [2 - (2 - Aminothiazol - 4 - yl) - 2 - hexyloxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer).

I.R. (Nujol): 3250, 1770, 1660, 1530 cm^{-1}.

Example 175

7 - [2 - (2 - Aminothiazol - 4 - yl) - 2 - (1 - carboxyethoxyimino)acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer).

I.R. (Nujol): 3260, 3160, 1770, 1670 cm^{-1}.

Example 176

7 - [2 - (2 - Aminothiazol - 4 - yl) - 2 - (1 - carboxy - 1 - methylethoxyimino)acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer).

I.R. (Nujol): 3300, 3200, 1770, 1670, 1640 cm^{-1}.

Example 177

7 - [2 - (2 - Aminothiazol - 4 - yl) - 2 - (3 - carboxypropoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer).

I.R. (Nujol): 3300, 1760, 1660 cm^{-1}.

Example 178

7 - [2 - (2 - Aminothiazol - 4 - yl) - 2 - ethoxycarbonylmethoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer).

I.R. (Nujol): 3250, 1770, 1670, 1530 cm^{-1}.

Example 179

Benzhydryl 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - (3 - benzhydryloxycarbonyl - 3 - tert - butoxycarbonylaminopropoxyimino)acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer).

I.R. (Nujol): 3300, 1780, 1719, 1680 cm^{-1}.

Example 180

Benzhydryl 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - (2 - benzhydryloxycarbonyl - 2 - tert - butoxycarbonylaminoethoxycarbonylmethoxyimino)acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer).

I.R. (Nujol): 3360, 1750 (broad) cm^{-1}.

Example 181

7 - [2 - (2 - Aminothiazol - 4 - yl) - 2 - (pyridin - 2 - ylmethoxyimino)acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer).

I.R. (Nujol): 3300, 1770, 1650, 1620, 1540 cm^{-1}.

Example 182

7 - [2 - (2 - Aminothiazol - 5 - yl) - 2 - methoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer).

I.R. (Nujol): 3300, 1780, 1645, 1580, 1515 cm^{-1}.

Example 183

7 - [2 - (2 - Aminothiazol - 4 - yl) - 2 - cyanomethoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer).

I.R. (Nujol): 3330, 2020, 1770, 1670, 1620 cm^{-1}.

Example 184

7 - [2 - (2 - Aminothiazol - 4 - yl) - 2 - (3 - carboxyallyloxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer).

I.R. (Nujol): 3250, 1760, 1690, 1650 cm^{-1}.

Example 185

7 - [2 - (2 - Amino - 5 - chlorothiazol - 4 - yl) - 2 - carboxymethoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer).

I.R. (Nujol): 3400, 3180, 1770, 1685, 1650, 1610 cm^{-1}.

Example 186

7 - [2 - (2 - Formamidothiazol - 4 - yl) - 2 - (O,O - diethylphosphonomethoxyimino)acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer).

I.R. (Nujol): 3160, 1775 (broad), 1680 (broad) cm^{-1}.

Example 187

7 - [2 - (2 - Aminothiazol - 4 - yl) - 2 - (2 - cyclopenten - 1 - yloxyimino)acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer).

I.R. (Nujol): 3270, 1765, 1650 cm^{-1}.

Example 188

7 - [2 - (5 - Amino - 1,2,4 - thiadiazol - 3 - yl) - 2 - methoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer).

I.R. (Nujol): 3350, 3250, 1770, 1670, 1620, 1530 cm^{-1}.

Example 189

Pivaloyloxymethyl 7 - [2 - (5 - amino - 1,2,4 - thiadiazol - 3 - yl) - 2 - methoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer).

I.R. (Nujol): 3400—3100, 1770, 1760, 1680, 1620, 1530 cm^{-1}.

Example 190

7 - [2 - (5 - Amino - 1,2,4 - thiadiazol - 3 - yl) - 2 - carboxymethoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer).

I.R. (Nujol): 3380, 3280, 1760, 1720, 1670 cm^{-1}.

Example 191

Benzhydryl 7 - [2 - (2 - formamidothiazol - 4 - yl) - 2 - methoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer).

I.R. (Nujol): 3250, 1780, 1710, 1700, 1660, 1540 cm^{-1}.

Example 192

Benzhydryl 7 - [2 - (2 - formamidothiazol - 4 - yl) - 2 - tert - butoxycarbonylmethoxyimino-acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer).

I.R. (Nujol): 3250, 1780, 1720, 1680, 1540 cm^{-1}.

Example 193

Benzhydryl 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - tert - butoxycarbonylmethoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer).

I.R. (Nujol): 3440, 3260, 3100, 1780, 1720, 1660, 1530 cm^{-1}.

Example 194

2 - (1 - tert - Butoxycarbonylethoxyimino) - 2 - (5 - amino - 1,2,4 - thiadiazol - 3 - yl)acetic acid (syn isomer) (2.2 g) was added to the stirred suspension of phosphorus pentachloride (1.6 g) in methylene chloride (22 ml) at −15°C, and the mixture was stirred for 30 minutes at −5 to −15°C. Dry diisopropyl ether was added to the reaction mixture at −10°C, and the precipitates were collected by filtration, washed with dry diisopropyl ether. On the other hand, trimethylsilylacetamide (5.4 g) was added to the stirred suspension of benzhydryl 7 - amino - 3 - vinyl - 3 - cephem - 4 - carboxylate hydrochloride (2.5 g) in methylene chloride (25 ml). To the solution obtained were added the above precipitates at −10°C and

stirred at −5 to −10°C for 40 minutes. Water was added to the resultant solution and the separated organic layer was washed with a saturated aqueous sodium bicarbonate and a saturated aqueous sodium chloride, dried over magnesium sulfate, and then evaporated to give benzhydryl 7 - [2 - (1 - tert - butoxycarbonyl-ethoxyimino) - 2 - (5 - amino - 1,2,4 - thiadiazol - 3 - yl)acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (2.51 g).

I.R. (Nujol): 1770, 1720, 1680, 1610 cm^{-1}.

Example 195

7 - [2 - (4 - tert - Butoxycarbonylaminothiazol - 2 - yl) - 2 - methoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer) (0.95 g) was obtained by reacting 7 - amino - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (0.7 g) with 2 - (4 - tert - butoxycarbonylaminothiazol - 2 - yl) - 2 - methoxyiminoacetic acid (syn isomer) (0.9 g) according to a similar manner to that of Example 1.

I.R. (Nujol): 3250, 1785, 1720, 1690, 1600, 1535 cm^{-1}.

N.M.R. δppm (DMSO-d_6): 1.45 (9H, s), 3.72 (2H, q, J=17Hz), 3.95 (3H, s), 5.18 (1H, d, J=5Hz), 5.28 (1H, d, J=11Hz), 5.52 (1H, d, J=17Hz), 5.82 (1H, dd, J=5Hz, 8Hz), 5.90 (1H, dd, J=11Hz, 17Hz), 7.28 (1H, s), 9.71 (1H, d, J=8Hz), 10.27 (1H, s).

Example 196

Trifluoroacetic acid (9.6 ml) was added to a solution of benzhydryl 7 - [2 - (1 - tert - butoxycarbonyl-ethoxyimino) - 2 - (5 - amino - 1,2,4 - thiadiazol - 3 - yl)acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylate (syn isomer) (2.4 g) in methylene chloride (5 ml) and anisole (2.4 ml) under ice-cooling, and the mixture was stirred for 1 hour at room temperature. The resultant solution was added dropwise to diisopropyl ether (100 ml) and the precipitates were collected by filtration. The precipitates were added to a mixture of water and ethyl acetate and then adjusted to pH 7.5 with 10% aqueous sodium hydroxide. The separated aqueous layer was saturated with sodium chloride and adjusted to pH 1.5 with 10% hydrochloric acid, followed by extraction with a mixed solvent of ethyl acetate and tetrahydrofuran (1:1 by volume). The extract was washed with a saturated aqueous sodium chloride and dried over magnesium sulfate.

Removal of the solvent gave 7 - [2 - (1 - carboxyethoxyimino) - 2 - (5 - amino - 1,2,4 - thiadiazol - 3 - yl)acetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer) (0.55 g).

I.R. (Nujol): 3330, 3200, 1770, 1670, 1610 cm^{-1}.

N.M.R. δppm (DMSO-d_6): 1.37 (3H, m), 3.70 (2H, m), 4.80 (1H, m), 5.07—6.07 (4H, m), 6.96 (1H, dd, J=12.0Hz, 18.0Hz), 8.17 (2H, broad s),
9.47 (d, J=8.0Hz) } (1H)
9.55 (d, J=8.0Hz) }

Example 197

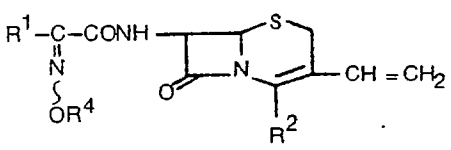
To ethanol (2 l) was added 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - carboxymethoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer) (70 g), and the mixture was stirred at 40°C for 30 minutes. The insoluble substance was collected by filtration and washed with ethanol. The washings and the filtrate were combined, and thereto was added water (4.2 l) at 40°C, followed by stirring at ambient temperature for an hour. The precipitates were collected by filtration to obtain crystalline trihydrate of 7 - [2 - (2 - aminothiazol - 4 - yl) - 2 - carboxymethoxyiminoacetamido] - 3 - vinyl - 3 - cephem - 4 - carboxylic acid (syn isomer) (61.6 g).

X-ray spectrum:

2θ°	I/I_0 (relative intensity)
29.9°	0.40
28.7	0.17
28.4	0.23
28.0	0.15
27.3	0.69
26.4	0.53
26.1	0.43
24.7	0.42
23.7	0.53
23.4	0.70
23.1	0.50
22.7	0.69
22.2	0.82
21.4	0.40
21.0	0.50
20.5	0.54
20.0	0.30
19.5	1.00
17.5	0.10
15.4	0.48
15.0	0.93
8.9	0.93
7.5	0.15
5.8	0.34

Claims for the Contracting States: BE CH DE FR GB IT LI LU NL SE

1. A compound of the formula:



in which

R^1 is aminothiazolyl which may have halogen, aminothiadiazolyl, protected aminothiazolyl which may have halogen or protected aminothiadiazolyl,

R^2 is carboxy or a protected carboxy group, and

R^4 is hydrogen, cyclo(C_3—C_7)alkenyl, C_2—C_7 alkynyl, C_2—C_7 alkenyl, C_2—C_7 alkenyl substituted by carboxy or a protected carboxy group, C_1—C_7 alkyl, or C_1—C_7 alkyl substituted by one or more substituent(s) selected from carboxy, a protected carboxy group, amino, a protected amino group, cyano, phosphono, a protected phosphono group and pyridyl and a pharmaceutically acceptable salt thereof.

2. A compound of claim 1, in which

R^1 is aminothiazolyl which may have halogen, aminothiadiazolyl, acylaminothiazolyl which may have halogen, di(C_1—C_7)alkylaminomethyleneaminothiadiazolyl,

R^4 is cyclo(C_3—C_7)alkenyl, C_2—C_7 alkynyl, C_2—C_7 alkenyl, C_2—C_7 alkenyl substituted by carboxy or an esterified carboxy, C_1—C_9 alkyl, C_1—C_7 alkyl substituted by one to two substituent(s) selected from carboxy, an esterified carboxy group, amino, acylamino, cyano, phosphono, an esterified phosphono group and pyridyl; and

R^2 is carboxy or an esterified carboxy group.

3. A compound of claim 2, which is syn isomer.

4. A compound of claim 3, in which R^1 is 2-aminothiazol-4-yl, 2-amino-5-halothiazol-4-yl, 2-aminothiazol-5-yl or 5-amino-1,2,4-thiadiazol-3-yl.

5. A compound of claim 4, in which R^4 is cyclo (C_3—C_7) alkenyl, C_2—C_7 alkynyl, C_2—C_7 alkenyl, carboxy(C_2—C_7)alkenyl, esterified carboxy(C_2—C_7)alkenyl, C_1—C_7 alkyl, carboxy(C_1—C_7)alkyl, esterified carboxy(C_1—C_7)alkyl, amino- and carboxy-substituted-C_1—C_7 alkyl, acylamino- and esterified carboxy-substituted-C_1—C_7 alkyl, cyano(C_1—C_7)alkyl, phosphono(C_1—C_7)alkyl, esterified phosphono(C_1—C_7)alkyl, or pyridyl(C_1—C_7)alkyl.

6. A compound of claim 5, in which R^2 is carboxy.

7. A compound of claim 6, in which R^4 is carboxy(C_1—C_7)alkyl.

8. A compound of claim 7, in which R^1 is 2-aminothiazol-4-yl.

9. A compound of claim 8, which is 7-[2-(2-aminothiazol-4-yl)-2-carboxymethoxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid or its hydrochloride or its disodium salt.

10. A compound of claim 8, which is trihydrate of 7-[2-(2-aminothiazol-4-yl)-2-carboxymethoxyimino-acetamido]-3-vinyl-3-cephem-4-carboxylic acid.

11. A compound of claim 6, in which R^1 is 2-aminothiazol-4-yl and R^4 is C_1—C_7 alkyl.

12. A compound of claim 11, which is 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid or its sodium salt.

13. A compound of claim 5, in which R^2 is mono- or di- or triphenyl(C_1—C_7)alkoxycarbonyl, C_1—C_7 alkanoyloxy(C_1—C_7)alkoxycarbonyl, amino- and carboxy-substituted-C_1—C_7 alkoxycarbonyl, or C_1—C_7 alkoxycarbonylamino- and mono- or di- or tri-phenyl(C_1—C_7)alkoxycarbonyl-substituted-C_1—C_7 alkoxy-carbonyl.

14. A compound of claim 13, in which R^4 is C_1—C_7 alkanoyloxy(C_1—C_7)alkoxycarbonyl(C_1—C_7)alkyl or C_1—C_7 alkoxycarbonyl(C_1—C_7)alkyl.

15. A compound of claim 14, in which R^1 is 2-aminothiazol-4-yl.

16. A compound of claim 15, which is pivaloyloxymethyl 7-[2-(2-aminothiazol-4-yl)-2-pivaloyloxy-methoxycarbonylmethoxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylate.

17. A compound of claim 13, in which R^1 is 2-aminothiazol-4-yl and R^4 is C_1—C_7 alkyl.

18. A compound of claim 17, which is pivaloyloxymethyl 7-[2-(2-aminothiazol-4-yl)-2-methoxyimino-acetamido]-3-vinyl-3-cephem-4-carboxylate.

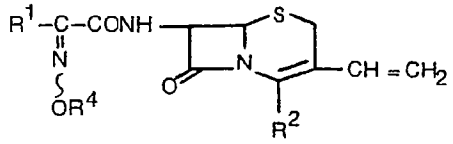
19. A compound of claim 3, which is

7-[2-(2-aminothiazol-4-yl)-2-{(1-methyl-3-pyridinio)methoxyimino}acetamido]-3-vinyl-3-cephem-4-carboxylate or its hydrochloride,

-[2-(2-aminothiazol-4-yl)-2-{(1-methyl-2-pyridinio)methoxyimino}acetamido]-3-vinyl-3-cephem-4-carboxylate or its hydrochloride,

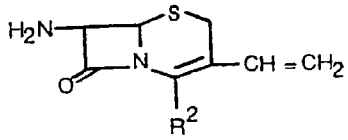
1-methyl-3-[1-(2-aminothiazol-4-yl)-1-{N-(4-benzhydryloxycarbonyl-3-vinyl-3-cephem-7-yl)-carbamoyl}methyleneaminooxymethyl]pyridnium methylsulfate or its hydrochloride, or 1-methyl-2-[1-(2-aminothiazol-4-yl)-1-{N-(4-benzhydryloxycarbonyl-3-vinyl-3-cephem-7-yl)carbamoyl}methylene-aminooxymethyl]pyridinium methylsulfate or its hydrochloride.

20. A process for preparing a compound of the formula:

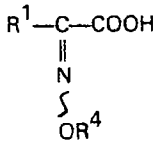


wherein R^1, R^2 and R^4 are as defined in claim 1 which comprises

(1) reacting a compound of the formula:

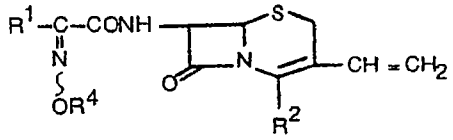


in which R^2 is as defined above, or its reactive derivative at the amino group or a salt thereof with a compound of the formula:



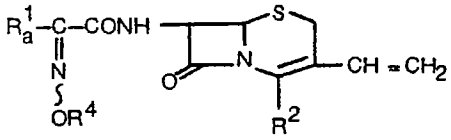
(III)

in which R^1 and R^4 are each as defined above, or its reactive derivative at the carboxy group or a salt thereof to give a compound of the formula:



in which R^1, R^2 and R^4 are each as defined above, or a salt thereof;

(2) subjecting a compound of the formula:

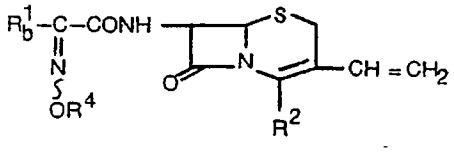


in which

R^1_a is protected aminothiazolyl which may have halogen or protected aminothiadiazolyl, and

R^2 and R^4 are each as defined above,

or a salt thereof to removal reaction of the amino-protective group to give a compound of the formula:



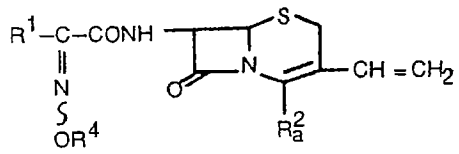
in which

R^1_b is aminothiazolyl which may have halogen or aminothiadiazolyl, and

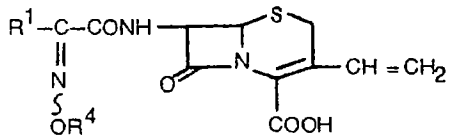
R^2 and R^4 are each as defined above,

or a salt thereof; or

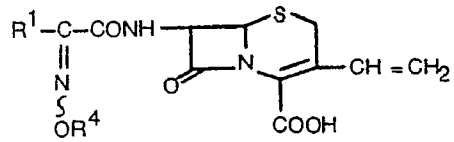
(3) subjecting a compound of the formula:



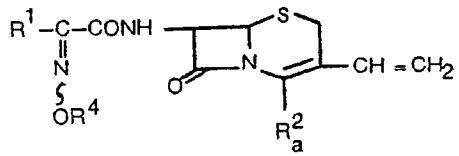
in which
R_a^2 is a protected carboxy group, and
R^1 and R^4 are each as defined above,
or a salt thereof to removal reaction of the carboxy-protective group to give a compound of the formula:



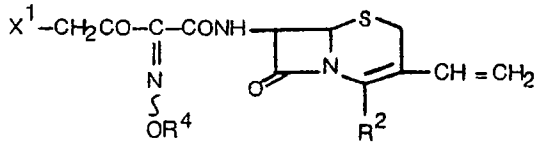
in which R^1 and R^4 are each as defined above, or a salt thereof; or
(4) introducing a carboxy-protective group into a compound of the formula:



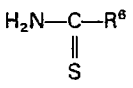
in which R^1 and R^4 are each as defined above, or a salt thereof to give a compound of the formula:



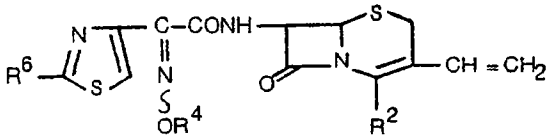
in which R^1, R_a^2 and R^4 are each as defined above, or a salt thereof; or
(5) reacting a compound of the formula:



in which
X^1 is halogen, and
R^2 and R^4 are each as defined above,
or a salt thereof with a compound of the formula:

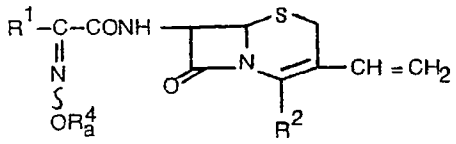


in which R^6 is amino or a protected amino group, to give a compound of the formula:



in which R^2, R^6 and R^4 are each as defined above, or a salt thereof; or

(6) subjecting a compound of the formula:

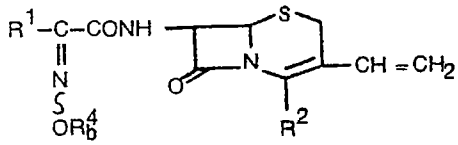


in which

R^4_a is C_1—C_7 alkyl substituted by a protected carboxy group or a protected phosphono group, or C_2—C_7 alkenyl substituted by a protected carboxy group, and

R^1 and R^2 are each as defined above,

or a salt thereof to removal reaction of the carboxy-protective group or the phosphono-protective group to give a compound of the formula:



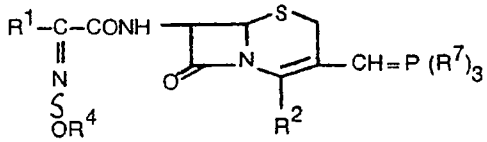
in which

R^4_b is C_1—C_7 alkyl substituted by carboxy or phosphono, or C_2—C_7 alkenyl substituted by carboxy, and

R^1 and R^2 are each as defined above,

or a salt thereof; or

(7) reacting a compound of the formula:

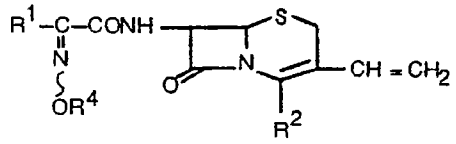


in which

R^7 is aryl, and

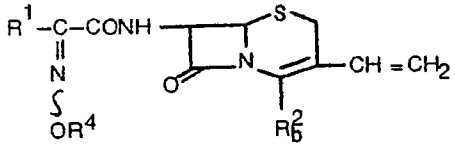
R^1, R^2 and R^4 are each as defined above,

or a salt thereof with formaldehyde to give a compound of the formula:



in which R^1, R^2 and R^4 are each as defined above, or a salt thereof; or

(8) subjecting a compound of the formula:

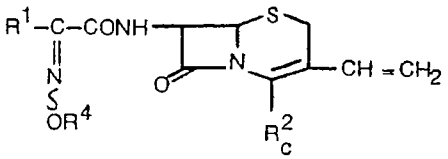


in which

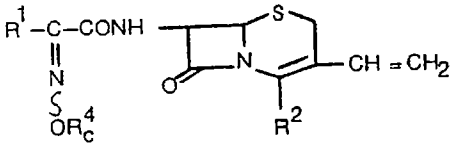
R^2_b is C_1—C_7 alkoxycarbonyl substituted by a protected amino and a protected carboxy groups, and

R^1 and R^4 are each as defined above,

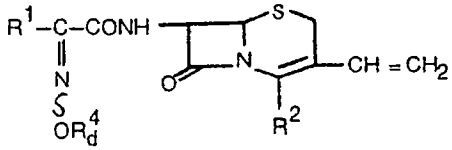
or a salt thereof to removal reaction of the amino- and carboxy-protective groups to give a compound of the formula:



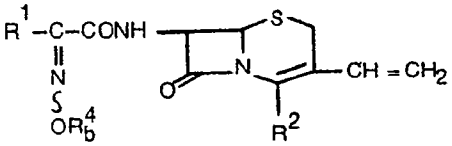
in which
R^2_c is C_1—C_7 alkoxycarbonyl substituted by amino and carboxy, and
R^1 and R^4 are each as defined above,
or a salt thereof; or
(9) subjecting a compound of the formula:



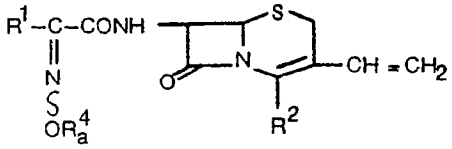
in which
R^4_c is C_1—C_7 alkoxycarbonyl(C_1—C_7)alkyl substituted by a protected amino and a protected carboxy groups, or C_1—C_7 alkyl substituted by a protected amino and a protected carboxy groups, and
R^1 and R^2 are each as defined above,
or a salt thereof to removal reaction of the amino- and carboxy-protective groups to give a compound of the formula:



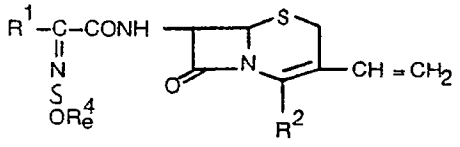
in which
R^4_d is C_1—C_7 alkoxycarbonyl(C_1—C_7)alkyl substituted by amino and carboxy, or C_1—C_7 alkyl substituted by amino and carboxy, and
R^1 and R^2 are each as defined above, or a salt thereof; or
(10) introducing a carboxy-protective group or a phosphono-protective group into a compound of the formula:



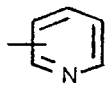
in which R^1, R^2 and R^4_b are each as defined above, or a salt thereof to give a compound of the formula:



in which R^1, R^2 and R^4_a are each as defined above, or a salt thereof; or
(11) reacting a compound of the formula:



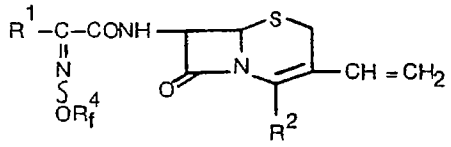
in which
R^4_e is C_1—C_7 alkyl substituted by a group of the formula:



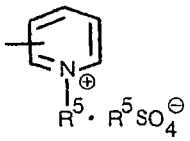
and
R^1 and R^2 are each as defined above,
or a salt thereof with a compound of the formula:

$$(R^5)_2SO_4$$

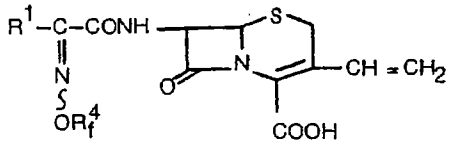
in which R^5 is C_1—C_7 alkyl, to give a compound of the formula:



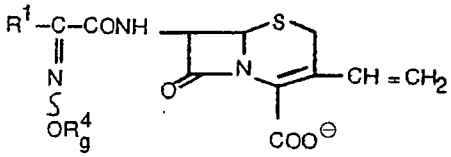
in which
R^4_f is C_1—C_7 alkyl substituted by a group of the formula:



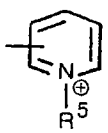
wherein
R^5 is as defined above, and
R^1 and R^2 are each as defined above,
or a salt thereof; or
(12) reacting a compound of the formula:



in which R^1 and R^4_f are each as defined above, or a salt thereof with a base to give a compound of the formula

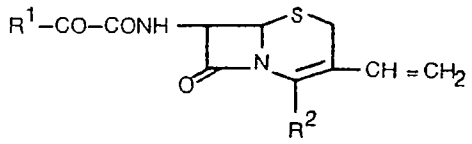


in which
R^4_g is C_1—C_7 alkyl substituted by a cation of the formula



wherein
R^5 is as defined above, and
R^1 is as defined above,
or a salt thereof; or

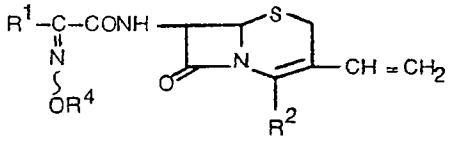
(13) reacting a compound of the formula:



in which R^1 and R^2 are each as defined above, or a salt thereof with a compound of the formula:

$$R^4ONH_2,$$

in which R^4 is as defined above, or a salt thereof to give a compound of the formula:



in which R^1, R^2 and R^4 are each as defined above or a salt thereof.

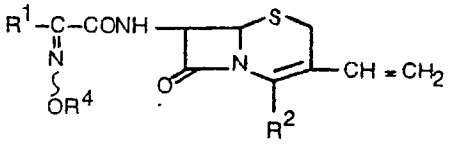
21. A pharmaceutical composition comprising, as active ingredients, the compound claimed in the claim 1, in admixture with pharmaceutically acceptable carriers.

22. A compound as claimed in either of claims 1 to 19 for use in the treatment of infectious diseases caused by pathogenic microorganisms.

23. Use of a compound as claimed in either of claims 1 to 19 for the preparation of a pharmaceutical composition for treating infectious diseases caused by pathogenic microorganisms.

Claims for the Contracting State: AT

1. A process for preparing a compound of the formula



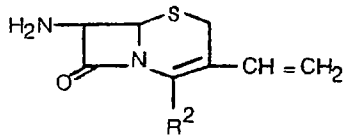
in which

R^1 is aminothiazolyl which may have halogen, aminothiadiazolyl, protected aminothiazolyl which may have halogen or protected aminothiadiazolyl,

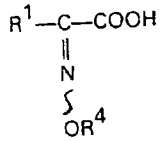
R^2 is carboxy or a protected carboxy group, and

R^4 is hydrogen, cyclo(C_3—C_7)alkenyl, C_2—C_7 alkynyl, C_2—C_7 alkenyl, C_2—C_7 alkenyl substituted by carboxy or a protected carboxy group, C_1—C_7 alkyl, or C_1—C_7 alkyl substituted by one or more substituent(s) selected from carboxy, a protected carboxy group, amino, a protected amino group, cyano, phosphono, a protected phosphono group and pyridyl and a pharmaceutically acceptable salt thereof, which comprises

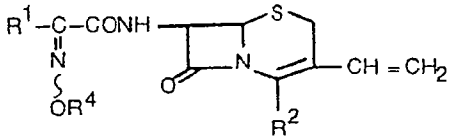
(1) reacting a compound of the formula:



in which R^2 is as defined above, or its reactive derivative at the amino group or a salt thereof with a compound of the formula:

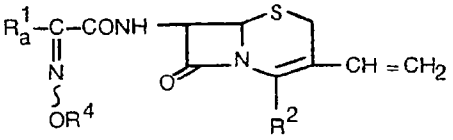


in which R^1 and R^4 are each as defined above, or its reactive derivative at the carboxy group or a salt thereof to give a compound of the formula:



in which R^1, R^2 and R^4 are each as defined above, or a salt thereof;

(2) subjecting a compound of the formula:

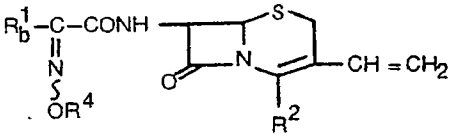


in which

R^1_a is protected aminothiazolyl which may have halogen or protected aminothiadiazolyl, and

R^2 and R^4 are each as defined above,

or a salt thereof to removal reaction of the amino-protective group to give a compound of the formula:



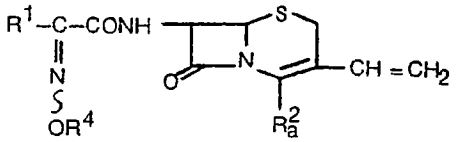
in which

R^1_b is aminothiazolyl which may have halogen or aminothiadiazolyl, and

R^2 and R^4 are each as defined above,

or a salt thereof; or

(3) subjecting a compound of the formula:

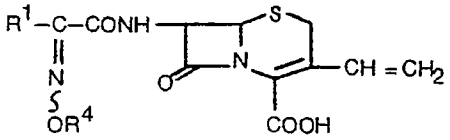


in which

R^2_a is a protected carboxy group, and

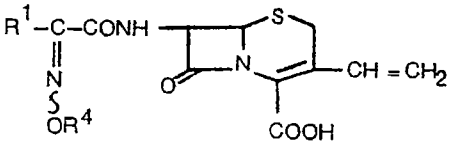
R^1 and R^4 are each as defined above,

or a salt thereof to removal reaction of the carboxy-protective group to give a compound of the formula:

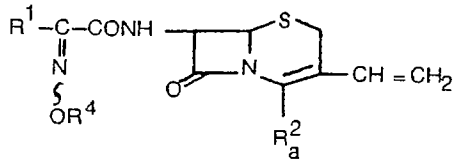


in which R^1 and R^4 are each as defined above, or a salt thereof; or

(4) introducing a carboxy-protective group into a compound of the formula:

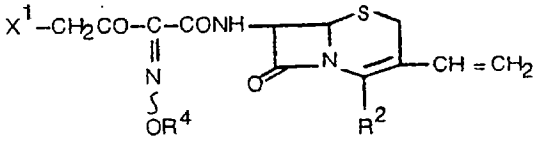


in which R^1 and R^4 are each as defined above, or a salt thereof to give a compound of the formula:



in which R^1, R^2_a and R^4 are each as defined above, or a salt thereof; or

(5) reacting a compound of the formula:

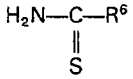


in which

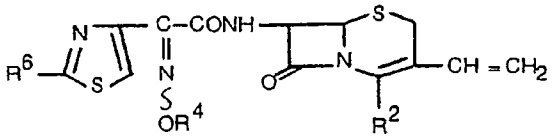
X^1 is halogen, and

R^2 and R^4 are each as defined above,

or a salt thereof with a compound of the formula:

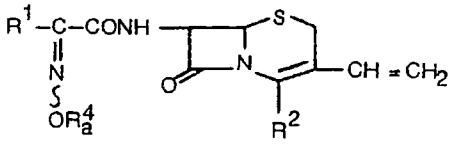


in which R^6 is amino or a protected amino group, to give a compound of the formula:



in which R^2, R^6 and R^4 are each as defined above, or a salt thereof; or

(6) subjecting a compound of the formula:

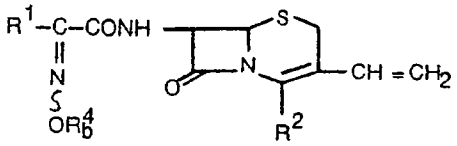


in which

R^4_a is C_1—C_7 alkyl substituted by a protected carboxy group or a protected phosphono group, or C_2—C_7 alkenyl substituted by a protected carboxy group, and

R^1 and R^2 are each as defined above,

or a salt thereof to removal reaction of the carboxy-protective group or the phosphono-protective group to give a compound of the formula:



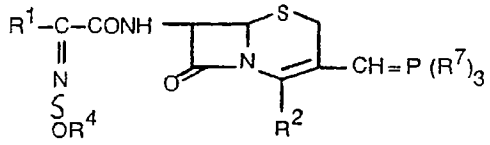
in which

R^4_b is C_1—C_7 alkyl substituted by carboxy or phosphono, or C_2—C_7 alkenyl substituted by carboxy, and

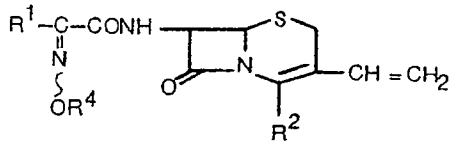
R^1 and R^2 are each as defined above,

or a salt thereof; or

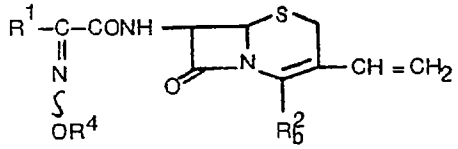
(7) reacting a compound of the formula:



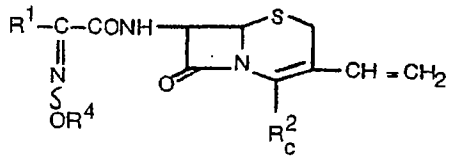
in which
R^7 is aryl, and
R^1, R^2 and R^4 are each as defined above,
or a salt thereof with formaldehyde to give a compound of the formula:



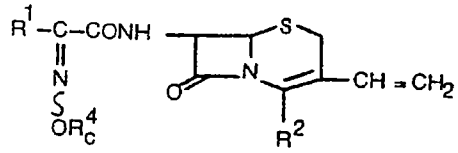
in which R^1, R^2 and R^4 are each as defined above, or a salt thereof; or
(8) subjecting a compound of the formula:



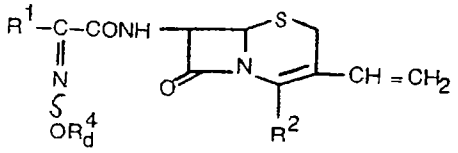
in which
R^2_b is C_1—C_7 alkoxycarbonyl substituted by a protected amino and a protected carboxy groups, and
R^1 and R^4 are each as defined above,
or a salt thereof to removal reaction of the amino- and carboxy-protective groups to give a compound of the formula:



in which
R^2_c is C_1—C_7 alkoxycarbonyl substituted by amino and carboxy, and
R^1 and R^4 are each as defined above,
or a salt thereof; or
(9) subjecting a compound of the formula:



in which
R^4_c is C_1—C_7 alkoxycarbonyl(C_1—C_7)alkyl substituted by a protected amino and a protected carboxy groups, or C_1—C_7 alkyl substituted by a protected amino and a protected carboxy groups, and
R^1 and R^2 are each as defined above,
or a salt thereof to removal reaction of the amino- and carboxy-protective groups to give a compound of the formula:

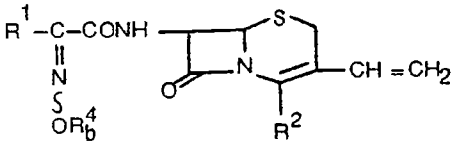


in which

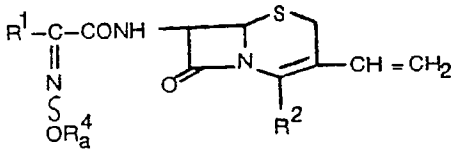
R^4_d is C_1—C_7 alkoxycarbonyl(C_1—C_7)alkyl substituted by amino and carboxy, or C_1—C_7 alkyl substituted by amino and carboxy, and

R^1 and R^2 are each as defined above, or a salt thereof; or

(10) introducing a carboxy-protective group or a phosphono-protective group into a compound of the formula:

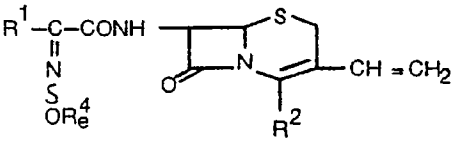


in which R^1, R^2 and R^4_b are each as defined above, or a salt thereof to give a compound of the formula:



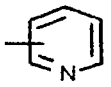
in which R^1, R^2 and R^4_a are each as defined above, or a salt thereof; or

(11) reacting a compound of the formula:



in which

R^4_e is C_1—C_7 alkyl substituted by a group of the formula:



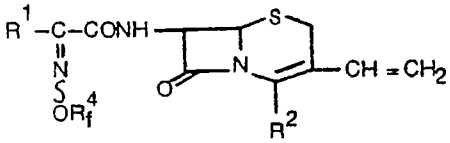
and

R^1 and R^2 are each as defined above,

or a salt thereof with a compound of the formula:

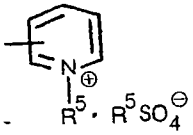
$$(R^5)_2SO_4$$

in which R^5 is C_1—C_7 alkyl, to give a compound of the formula:

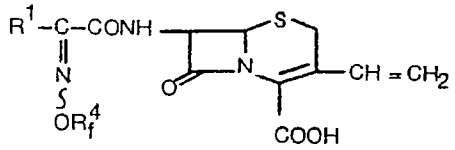


in which

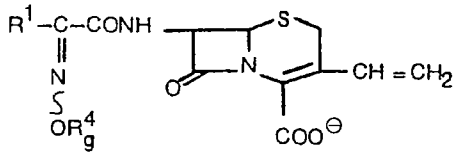
R^4_f is C_1—C_7 alkyl substituted by a group of the formula:



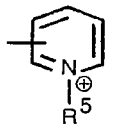
wherein
R^5 is as defined above, and
R^1 and R^2 are each as defined above,
or a salt thereof; or
(12) reacting a compound of the formula:



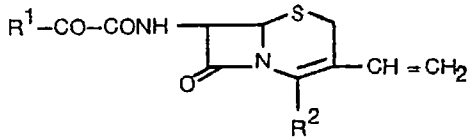
in which R^1 and R^4_f are each as defined above, or a salt thereof with a base to give a compound of the formula



in which
R^4_g is C_1—C_7 alkyl substituted by a cation of the formula



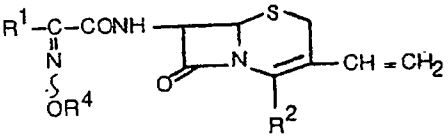
wherein
R^5 is as defined above, and
R^1 is as defined above,
or a salt thereof; or
(13) reacting a compound of the formula:



in which R^1 and R^2 are each as defined above, or a salt thereof with a compound of the formula:

$$R^4ONH_2,$$

in which R^4 is as defined above, or a salt thereof to give a compound of the formula:



in which R^1, R^2 and R^4 are each as defined above or a salt thereof.

2. A process of claim 1, in which
R^1 is aminothiazolyl which may have halogen, aminothiadiazolyl, acylaminothiazolyl which may have halogen, di(C_1—C_7)alkylaminomethyleneaminothiadiazolyl,
R^4 is cyclo(C_3—C_7)alkenyl, C_2—C_7 alkynyl, C_2—C_7 alkenyl, C_2—C_7 alkenyl substituted by carboxy or an esterified carboxy, C_1—C_9 alkyl, C_1—C_7 alkyl substituted by one to two substituent(s) selected from carboxy, an esterified carboxy group, amino, acylamino, cyano, phosphono, an esterified phosphono group and pyridyl; and
R^2 is carboxy or an esterified carboxy group.

3. A process of claim 2, in which the syn isomer is prepared.

4. A process of claim 3, in which R^1 is 2-aminothiazol-4-yl, 2-amino-5-halothiazol-4-yl, 2-aminothiazol-5-yl or 5-amino-1,2,4-thiadiazol-3-yl.

5. A process of claim 4, in which R^4 is cyclo (C_3—C_7) alkenyl, C_2—C_7 alkynyl, C_2—C_7 alkenyl, carboxy(C_2—C_7)alkenyl, esterified carboxy(C_2—C_7)alkenyl, C_1—C_7 alkyl, carboxy(C_1—C_7)alkyl, esterified carboxy(C_1—C_7)alkyl, amino- and carboxy-substituted-C_1—C_7 alkyl, acylamino- and esterified carboxy-substituted-C_1—C_7 alkyl, cyano(C_1—C_7)alkyl, phosphono(C_1—C_7)alkyl, esterified phosphono(C_1—C_7)alkyl, or pyridyl(C_1—C_7)alkyl.

6. A process of claim 5, in which R^2 is carboxy.

7. A process of claim 6, in which R^4 is carboxy(C_1—C_7)alkyl.

8. A process of claim 7, in which R^1 is 2-aminothiazol-4-yl.

9. A process of claim 8, in which 7-[2-(2-aminothiazol-4-yl)-2-carboxymethoxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid or its hydrochloride or its disodium salt is prepared.

10. A process of claim 8, in which the trihydrate of 7-[2-(2-aminothiazol-4-yl)-2-carboxymethoxyimino-acetamido]-3-vinyl-3-cephem-4-carboxylic acid is prepared.

11. A process of claim 6, in which R^1 is 2-aminothiazol-4-yl and R^4 is C_1—C_7 alkyl.

12. A process of claim 11, in which 7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid or its sodium salt is prepared.

13. A process of claim 5, in which R^2 is mono- or di- or triphenyl(C_1—C_7)alkoxycarbonyl, C_1—C_7 alkanoyloxy(C_1—C_7)alkoxycarbonyl, amino- and carboxy-substituted-C_1—C_7 alkoxycarbonyl, or C_1—C_7 alkoxycarbonylamino- and mono- or di- or tri-phenyl(C_1—C_7)alkoxycarbonyl-substituted-C_1—C_7 alkoxy-carbonyl.

14. A process of claim 13, in which R^4 is C_1—C_7 alkanoyloxy(C_1—C_7)alkoxycarbonyl(C_1—C_7)alkyl or C_1—C_7 alkoxycarbonyl(C_1—C_7)alkyl.

15. A process of claim 14, in which R^1 is 2-aminothiazol-4-yl.

16. A process of claim 15, in which pivaloyloxymethyl 7-[2-(2-aminothiazol-4-yl)-2-pivaloyloxy-methoxycarbonylmethoxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylate is prepared.

17. A process of claim 13, in which R^1 is 2-aminothiazol-4-yl and R^4 is C_1—C_7 alkyl.

18. A process of claim 17, in which pivaloyloxymethyl 7-[2-(2-aminothiazol-4-yl)-2-methoxyimino-acetamido]-3-vinyl-3-cephem-4-carboxylate is prepared.

19. A process of claim 3, in which

7-[2-(2-aminothiazol-4-yl)-2-{(1-methyl-3-pyridinio)methoxyimino}acetamido]-3-vinyl-3-cephem-4-carboxylate or its hydrochloride,

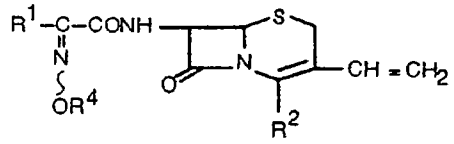
7-[2-(2-aminothiazol-4-yl)-2-{(1-methyl-2-pyridinio)methoxyimino}acetamido]-3-vinyl-3-cephem-4-carboxylate or its hydrochloride,

1-methyl-3-[1-(2-aminothiazol-4-yl)-1-{N-(4-benzhydryloxycarbonyl-3-vinyl-3-cephem-7-yl)-carbamoyl}methyleneaminooxymethyl]pyridnium methylsulfate or its hydrochloride, or

1-methyl-2-[1-(2-aminothiazol-4-yl)-1-{N-(4-benzhydryloxycarbonyl-3-vinyl-3-cephem-7-yl)-carbamoyl}methyleneaminooxymethyl]pyridinium methylsulfate or its hydrochloride is prepared.

Patentansprüche für die Vertragsstaaten: BE CH DE FR GB IT LI LU NL SE

1. Verbindung der Formel



worin R^1 Aminothiazolyl, welches Halogen aufweisen kann, Aminothiadiazolyl, geschütztes Aminothiazolyl, welches Halogen aufweisen kann, oder geschütztes Aminothiadiazolyl ist,

R^2 Carboxy oder eine geschützte Carboxygruppe ist, und

R^4 Wasserstoff, Cyclo(C_3—C_7)alkenyl, (C_2—C_7)Alkinyl, (C_2—C_7)Alkenyl, durch Carboxy oder eine geschützte Carboxygruppe substituiertes (C_2—C_7)Alkenyl, (C_1—C_7)Alkyl oder durch einen oder mehrere Substituenten, ausgewählt aus Carboxy, eine geschützte Carboxygruppe, Amino, eine geschützte Aminogruppe, Cyano, Phosphono, eine geschützte Phosphonogruppe und Pyridyl, substituiertes (C_1—C_7)Alkyl ist, und ein pharmazeutisch annehmbares Salz davon.

2. Verbindung nach Anspruch 1, worin

R^1 Aminothiazolyl, welches Halogen aufweisen kann, Aminothiadiazolyl, Acylaminothiazolyl, welches Halogen aufweisen kann, Di(C_1—C_7)alkylaminomethylenaminothiadiazolyl ist,

R^4 Cyclo(C_3—C_7)alkenyl, (C_2—C_7)Alkinyl, (C_2—C_7)Alkenyl, durch Carboxy oder ein verestertes Carboxy substituiertes (C_2—C_7)Alkenyl, (C_1—C_7)Alkyl, durch einen oder zwei Substituenten, ausgewählt aus Carboxy, einer veresterten Carboxygruppe, Amino, Acylamino, Cyano, Phosphono, einer veresterten Phosphonogruppe und Pyridyl, substituiertes (C_1—C_7)Alkyl ist; und

R^2 Carboxy oder eine veresterte Carboxygruppe ist.

3. Verbindung nach Anspruch 2, welche das syn-Isomer ist.

4. Verbindung nach Anspruch 3, worin R^1 2-Aminothiazol-4-yl, 2-Amino-5-halogenthiazol-4-yl, 2-Aminothiazol-5-yl oder 5-Amino-1,2,4-thiadiazol-3-yl ist.

5. Verbindung nach Anspruch 4, worin R^4 Cyclo(C_3—C_7)alkenyl, (C_2—C_7)Alkinyl, (C_2—C_7)Alkenyl, Carboxy(C_2—C_7)alkenyl, verestertes Carboxy(C_2—C_7)alkenyl, (C_1—C_7)Alkyl, Carboxy(C_1—C_7)alkyl, verestertes Carboxy(C_1—C_7)alkyl, Amino- und Carboxy-substituiertes (C_1—C_7)Alkyl, Acylamino- und Estercarboxy-substituiertes (C_1—C_7)Alkyl, Cyano(C_1—C_7)alkyl, Phosphono(C_1—C_7)alkyl, verestertes Phosphono(C_1—C_7)alkyl oder Pyridyl(C_1—C_7)alkyl ist.

6. Verbindung nach Anspruch 5, worin R^2 Carboxy ist.

7. Verbindung nach Anspruch 6, worin R^4 Carboxy(C_1—C_7)alkyl ist.

8. Verbindung nach Anspruch 7, worin R^1 2-Aminothiazol-4-yl ist.

9. Verbindung nach Anspruch 8, welche 7-[2-(2-Aminothiazol-4-yl)-2-carboxymethoxyiminoacetamido]-3-vinyl-3-cephem-4-carbonsäure oder ihr Hydrochlorid oder ihr Dinatriumsalz ist.

10. Verbindung nach Anspruch 8, welche das Trihydrat von 7-[2-(2-Aminothiazol-4-yl)-2-carboxymethoxyiminoacetamido]-3-vinyl-3-cephem-4-carbonsäure ist.

11. Verbindung nach Anspruch 6, worin R^1 2-Aminothiazol-4-yl ist und R^4 (C_1—C_7)Alkyl ist.

12. Verbindung nach Anspruch 11, welche 7-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-vinyl-3-cephem-4-carbonsäure oder ihr Natriumsalz ist.

13. Verbindung nach Anspruch 5, worin R^2 Mono- oder Di- oder Triphenyl(C_1—C_7)alkoxycarbonyl, (C_1—C_7)Alkanoyloxy(C_1—C_7)alkoxycarbonyl, Amino- und Carboxy-substituiertes (C_1—C_7)Alkoxycarbonyl oder (C_1—C_7)Alkoxycarbonylamino- und Mono- oder Di- oder Triphenyl(C_1—C_7)alkoxycarbonyl-substituiertes (C_1—C_7)Alkoxycarbonyl ist.

14. Verbindung nach Anspruch 13, worin R^4 (C_1—C_7)Alkanoyloxy(C_1—C_7)alkoxycarbonyl(C_1—C_7)alkyl oder (C_1—C_7)Alkoxycarbonyl(C_1—C_7)alkyl ist.

15. Verbindung nach Anspruch 14, worin R^1 2-Aminothiazol-4-yl ist.

16. Verbindung nach Anspruch 15, welche Pivaloyloxymethyl-7-[2-(2-aminothiazol-4-yl)-2-pivaloyloxymethoxycarbonylmethoxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylat ist.

17. Verbindung nach Anspruch 13, worin R^1 2-Aminothiazol-4-yl ist und R^4 (C_1—C_7)Alkyl ist.

18. Verbindung nach Anspruch 17, welche Pivaloyloxymethyl-7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylat ist.

19. Verbindung nach Anspruch 3, welche

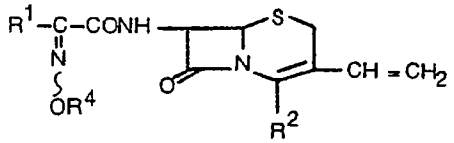
7-[2-(2-Aminothiazol-4-yl)-2-{(1-methyl-3-pyridinio)-methoxyimino}acetamido]-3-vinyl-3-cephem-4-carboxylat oder ihr Hydrochlorid,

7-[2-(2-Aminothiazol-4-yl)-2-{(1-methyl-2-pyridinio)-methoxyimino}acetamido]-3-vinyl-3-cephem-4-carboxylat oder ihr Hydrochlorid,

1-Methyl-3-[1-(2-aminothiazol-4-yl)-1-{N-(4-benzhydryloxycarbonyl-3-vinyl-3-cephem-7-yl)-carbamoyl}methylenaminooxymethyl]-pyridinium-methylsulfat oder ihr Hydrochlorid, oder

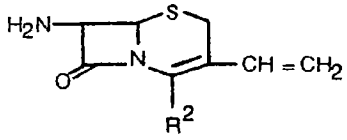
1-Methyl-2-[1-(2-aminothiazol-4-yl)-1-{N-(4-benzhydryloxycarbonyl-3-vinyl-3-cephem-7-yl)carbamoyl}methylenaminooxymethyl]pyridinium-methylsulfat oder ihr Hydrochlorid ist.

20. Verfahren zur Herstellung einer Verbindung der Formel

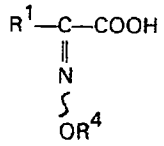


worin R^1, R^2 und R^4 wie in Anspruch 1 definiert sind, und eines pharmazeutisch annehmbaren Salzes davon, durch

(1) Reagieren einer Verbindung der Formel

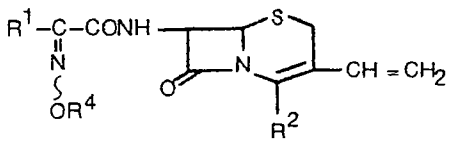


worin R^2 wie oben definiert ist,
oder ihres reaktiven Derivats an der Aminogruppe oder eines Salzes davon mit einer Verbindung der Formel

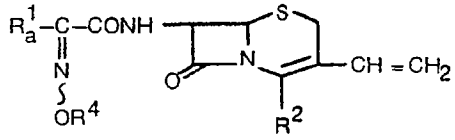


(III)

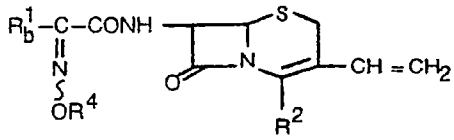
worin R^1 und R^4 jeweils wie oben definiert sind,
oder ihrem reaktiven Derivat an der Carboxygruppe oder einem Salz davon unter Bildung einer Verbindung der Formel



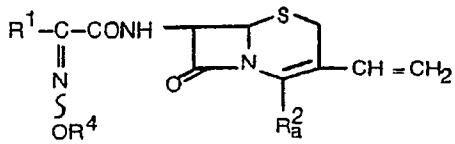
worin R^1, R^2 und R^4 jeweils wie oben definiert sind,
oder eines Salzes davon;
(2) Unterwerfen einer Verbindung der Formel



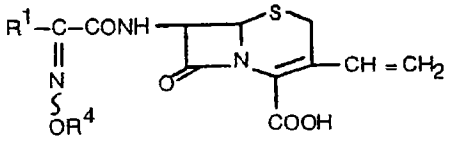
worin
R_a^1 geschütztes Aminothiazolyl ist, welches Halogen aufweisen kann, oder geschütztes Aminothiadiazolyl ist, und
R^2 und R^4 jeweils wie oben definiert sind,
oder eines Salzes davon der Entfernungsreaktion der Aminoschutzgruppe unter Bildung einer Verbindung der Formel



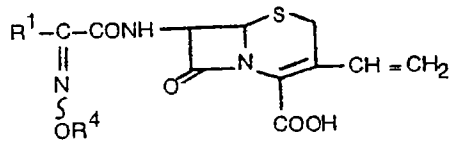
worin
R_b^1 Aminothiazolyl, welches Halogen aufweisen kann,
oder Aminothiadiazolyl ist, und
R^2 und R^4 jeweils wie oben definiert sind,
oder eines Salzes davon; oder
(3) Unterwerfen einer Verbindung der Formel



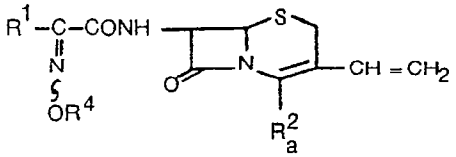
worin
R_a^2 eine geschützte Carboxygruppe ist, und
R^1 und R^4 jeweils wie oben definiert sind,
oder eines Salzes davon der Entfernungsreaktion der Carboxyschutzgruppe unter Bildung einer Verbindung der Formel



worin R^1 und R^4 jeweils wie oben definiert sind,
oder eines Salzes davon; oder
(4) Einführen einer Carboxyschutzgruppe in eine Verbindung der Formel

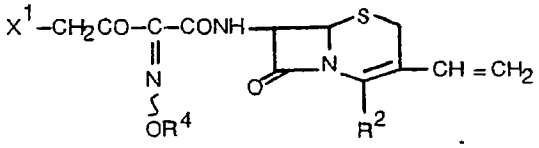


worin R^1 und R^4 jeweils wie oben definiert sind,
oder ein Salz davon unter Bildung einer Verbindung der Formel

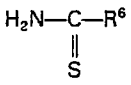


worin R^1, R^2_a und R^4 jeweils wie oben definiert sind,
oder eines Salzes davon; oder

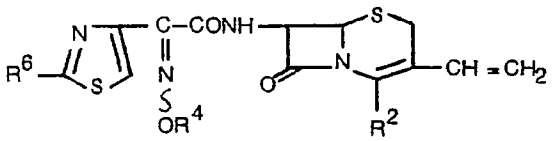
(5) Reagieren einer Verbindung der Formel



worin X^1 Halogen ist, und
R^2 und R^4 jeweils wie oben definiert sind,
oder eines Salzes davon mit einer Verbindung der Formel

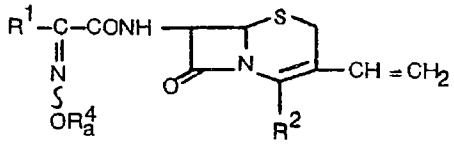


worin R^6 Amino oder eine geschützte Aminogruppe ist, unter Bildung einer Verbindung der Formel

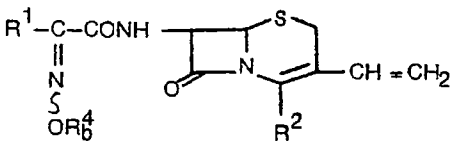


worin R^2, R^6 und R^4 jeweils wie oben definiert sind,
oder eines Salzes davon; oder

(6) Unterwerfen einer Verbindung der Formel

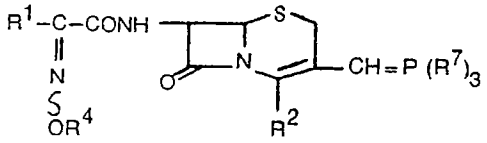


worin
R^4_a durch eine geschützte Carboxygruppe oder eine gegeschützte Phosphonogruppe substituiertes (C_1—C_7)Alkyl oder durch eine geschützte Carboxygruppe substituiertes (C_2—C_7)Alkenyl ist, und
R^1 und R^2 jeweils wie oben definiert sind,
oder eines Salzes davon der Entfernungsreaktion der Carboxyschutzgruppe oder der Phosphonoschutzgruppe unter Bildung einer Verbindung der Formel



worin
R^4_b durch Carboxy oder Phosphono substituiertes (C_1—C_7)Alkyl oder durch Carboxy substituiertes (C_2—C_7)Alkenyl ist, und
R^1 und R^2 jeweils wie oben definiert sind,
oder eines Salzes davon; oder

(7) Reagieren einer Verbindung der Formel

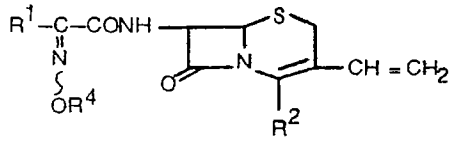


worin

R^7 Aryl ist und

R^1, R^2 und R^4 jeweils wie oben definiert sind,

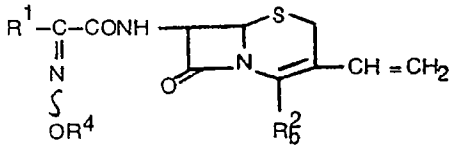
oder eines Salzes davon mit Formaldehyd unter Bildung einer Verbindung der Formel



worin R^1, R^2 und R^4 jeweils wie oben definiert sind,

oder eines Salzes davon; oder

(8) Unterwerfen einer Verbindung der Formel

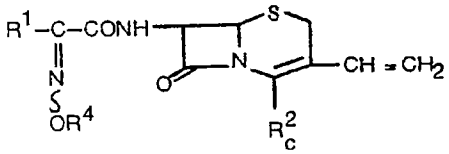


worin

R_b^2 durch eine geschützte Amino- und eine geschützte Carboxygruppe substituiertes (C_1—C_7)Alkoxycarbonyl ist, und

R^1 und R^4 jeweils wie oben definiert sind,

oder eines Salzes davon der Entfernungsreaktion der Amino- und Carboxyschutzgruppe unter Bildung einer Verbindung der Formel



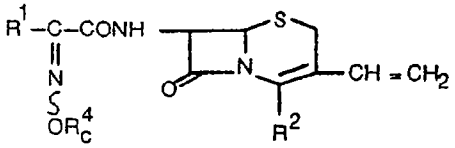
worin

R_c^2 durch Amino und Carboxy substituiertes (C_1—C_7)Alkoxycarbonyl ist, und

R^1 und R^4 jeweils wie oben definiert sind,

oder eines Salzes davon; oder

(9) Unterwerfen einer Verbindung der Formel

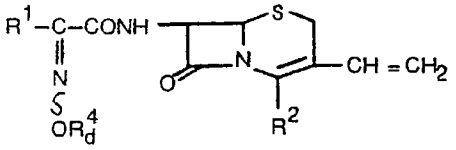


worin

R_c^4 durch eine geschützte Amino- und eine geschützte Carboxygruppe substituiertes (C_1—C_7)Alkoxycarbonyl(C_1—C_7)alkyl oder durch eine geschützte Amino- und eine geschützte Carboxygruppe substituiertes (C_1—C_7)Alkyl ist, und

R^1 und R^2 jeweils wie oben definiert sind,

oder eines Salzes davon der Entfernungsreaktion der Amino- und Carboxyschutzgruppe unter Bildung einer Verbindung der Formel

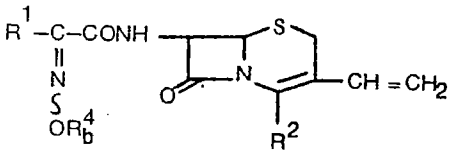


worin R^4_d durch Amino und Carboxy substituiertes (C_1—C_7)Alkoxycarbonyl(C_1—C_7)alkoxy oder durch Amino und Carboxy substituiertes (C_1—C_7)Alkyl ist, und

R^1 und R^2 jeweils wie oben definiert sind,

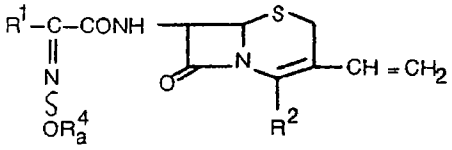
oder eines Salzes davon; oder

(10) Einführen einer Carboxyschutzgruppe oder einer Phosphonoschutzgruppe in eine Verbindung der Formel



worin R^1, R^2 und R^4_b jeweils wie oben definiert sind,

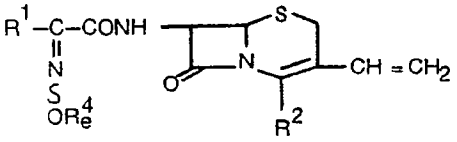
oder ein Salz davon unter Bildung einer Verbindung der Formel



worin R^1, R^2 und R^4_a jeweils wie oben definiert sind,

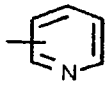
oder einer Salzes davon; oder

(11) Reagieren einer Verbindung der Formel



worin

R^4_e durch eine Gruppe der Formel



substituiertes (C_1—C_7)Alkyl ist, und

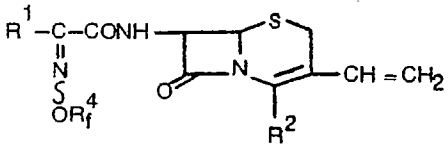
R^1 und R^2 jeweils wie oben definiert sind,

oder eines Salzes davon mit einer Verbindung der Formel

$$(R^5)_2SO_4$$

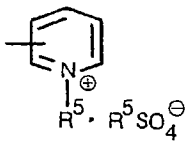
worin R^5 (C_1—C_7)Alkyl ist,

unter Bildung einer Verbindung der Formel



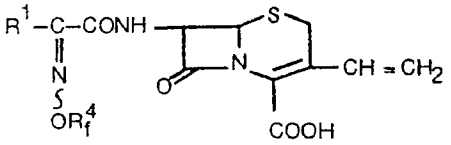
worin

R^4_f durch eine Gruppe der Formel

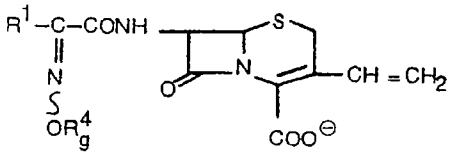


substituiertes (C_1—C_7)Alkyl ist, worin
R^5 wie oben definiert ist, und
R^1 und R^2 jeweils wie oben definiert sind,
oder eines Salzes davon; oder

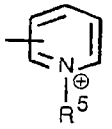
(12) Reagieren einer Verbindung der Formel



worin R^1 und R^4_f jeweils wie oben definiert sind,
oder eines Salzes davon mit einer Base unter Bildung einer Verbindung der Formel

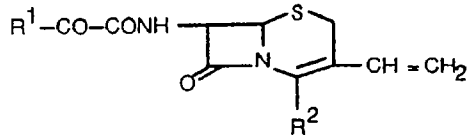


worin
R^4_g durch ein Kation der Formel

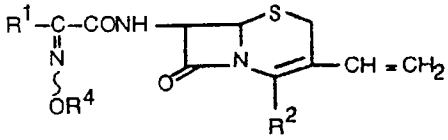


substituiertes (C_1—C_7)Alkyl ist, worin
R^5 wie oben definiert ist, und
R^1 wie oben definiert ist,
oder eines Salzes davon; oder

(13) Reagieren einer Verbindung der Formel



worin R^1 und R^2 jeweils wie oben definiert sind,
oder eines Salzes davon mit einer Verbindung der Formel R^4ONH_2, worin R^4 wie oben definiert ist, oder einem Salz davon unter Bildung einer Verbindung der Formel



worin R^1, R^2 und R^4 jeweils wie oben definiert sind,
oder eines Salzes davon.

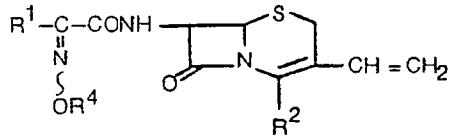
21. Pharmazeutische Zusammensetzung, enthaltend als aktive Bestandteile die in Anspruch 1 beanspruchte Verbindung in Vermischung mit pharmazeutisch annehmbaren Trägern.

22. Verbindung nach einem der Ansprüche 1 bis 19 zur Verwendung in der Behandlung von durch pathogene Mikroorganismen verursachte Infektionskrankheiten.

23. Verwendung einer Verbindung nach einem der Ansprüche 1 bis 19 zur Herstellung einer pharmazeutischen Zusammensetzung zur Behandlung von durch pathogene Mikroorganismen verursachten Infektionskrankheiten.

Patentansprüche für den Vertragsstaat: AT

1. Verfahren zur Herstellung einer Verbindung der Formel



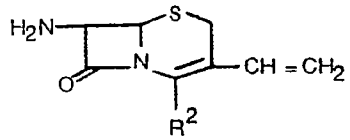
worin

R^1 Aminothiazolyl, welches Halogen aufweisen kann, Aminothiadiazolyl, geschütztes Aminothiazolyl, welches Halogen aufweisen kann, oder geschütztes Aminothiadiazolyl ist,

R^2 Carboxy oder eine geschützte Carboxygruppe ist, und

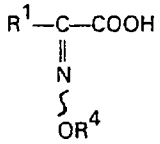
R^4 Wasserstoff, Cyclo(C_3—C_7)alkenyl, (C_2—C_7)Alkinyl, (C_2—C_7)Alkenyl, durch Carboxy oder eine geschützte Carboxygruppe substituiertes (C_2—C_7)Alkenyl, (C_1—C_7)Alkyl oder durch einen oder mehrere Substituenten, ausgewählt aus Carboxy, eine geschützte Carboxygruppe, Amino, eine geschützte Aminogruppe, Cyano, Phosphono, eine geschützte Phosphonogruppe und Pyridyl, substituiertes (C_1—C_7)Alkyl ist, und ein pharmazeutisch annehmbares Salz davon, durch

(1) Reagieren einer Verbindung der Formel



worin R^2 wie oben definiert ist,

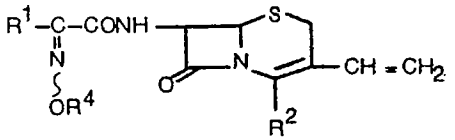
oder ihres reaktiven Derivats an der Aminogruppe oder eines Salzes davon mit einer Verbindung der Formel



(III)

worin R^1 und R^4 jeweils wie oben definiert sind,

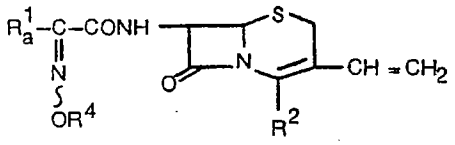
oder ihrem reaktiven Derivat an der Carboxygruppe oder einem Salz davon unter Bildung einer Verbindung der Formel



worin R^1, R^2 und R^4 jeweils wie oben definiert sind,

oder eines Salzes davon;

(2) Unterwerfen einer Verbindung der Formel

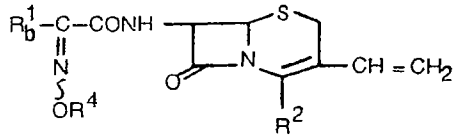


worin

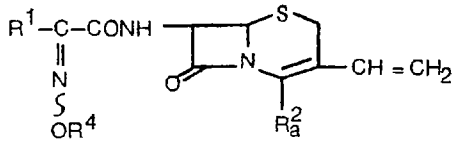
R^1_a geschütztes Aminothiazolyl ist, welches Halogen aufweisen kann, oder geschütztes Aminothiadiazolyl ist, und

R^2 und R^4 jeweils wie oben definiert sind,

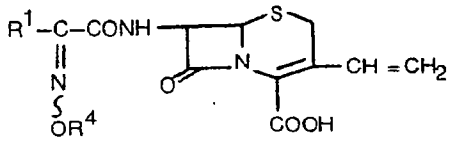
oder eines Salzes davon der Entfernungsreaktion der Aminoschutzgruppe unter Bildung einer Verbindung der Formel



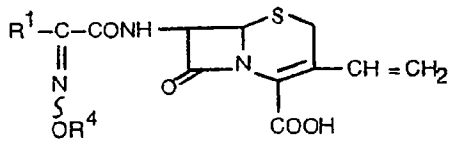
worin
R_b^1 Aminothiazolyl, welches Halogen aufweisen kann,
oder Aminothiadiazolyl ist, und
R^2 und R^4 jeweils wie oben definiert sind,
oder eines Salzes davon; oder
(3) Unterwerfen einer Verbindung der Formel



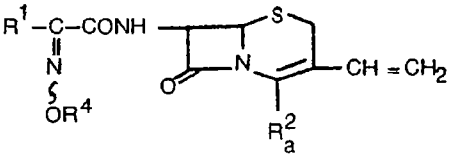
worin
R_a^2 eine geschützte Carboxygruppe ist, und
R^1 und R^4 jeweils wie oben definiert sind,
oder eines Salzes davon der Entfernungsreaktion der Carboxyschutzgruppe unter Bildung einer Verbindung der Formel



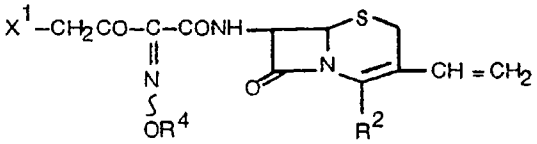
worin R^1 und R^4 jeweils wie oben definiert sind,
oder eines Salzes davon; oder
(4) Einführen einer Carboxyschutzgruppe in eine Verbindung der Formel



worin R^1 und R^4 jeweils wie oben definiert sind,
oder ein Salz davon unter Bildung einer Verbindung der Formel

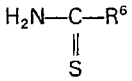


worin R^1, R_a^2 und R^4 jeweils wie oben definiert sind,
oder eines Salzes davon; oder
(5) Reagieren einer Verbindung der Formel

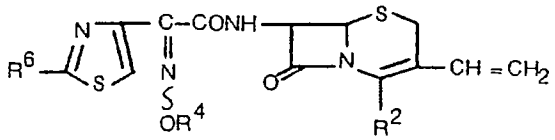


worin X^1 Halogen ist, und

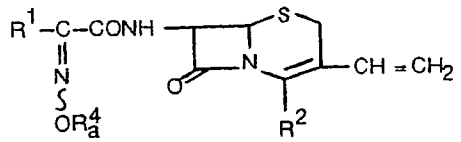
R^2 und R^4 jeweils wie oben definiert sind,
oder eines Salzes davon mit einer Verbindung der Formel



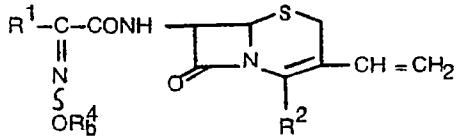
worin R^6 Amino oder eine geschützte Aminogruppe ist, unter Bildung einer Verbindung der Formel



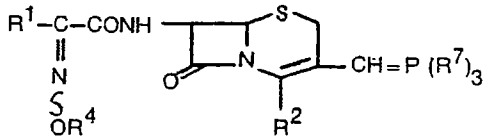
worin R^2, R^6 und R^4 jeweils wie oben definiert sind,
oder eines Salzes davon; oder
(6) Unterwerfen einer Verbindung der Formel



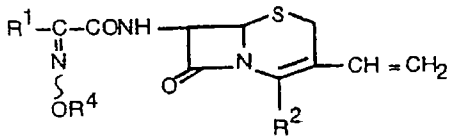
worin
R^4_a durch eine geschützte Carboxygruppe oder eine geschützte Phosphonogruppe substituiertes $(C_1—C_7)$Alkyl oder durch eine geschützte Carboxygruppe substituiertes $(C_2—C_7)$Alkenyl ist, und
R^1 und R^2 jeweils wie oben definiert sind,
oder eines Salzes davon der Entfernungsreaktion der Carboxyschutzgruppe oder der Phosphonoschutzgruppe unter Bildung einer Verbindung der Formel



worin
R^4_b durch Carboxy oder Phosphono substituiertes $(C_1—C_7)$Alkyl oder durch Carboxy substituiertes $(C_2—C_7)$Alkenyl ist, und
R^1 und R^2 jeweils wie oben definiert sind,
oder eines Salzes davon; oder
(7) Reagieren einer Verbindung der Formel

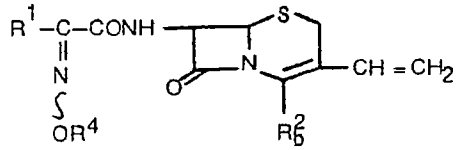


worin
R^7 Aryl ist und
R^1, R^2 und R^4 jeweils wie oben definiert sind,
oder eines Salzes davon mit Formaldehyd unter Bildung einer Verbindung der Formel

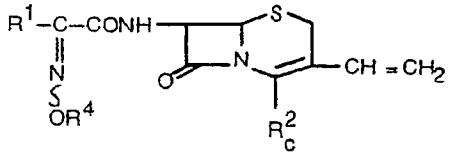


worin R^1, R^2 und R^4 jeweils wie oben definiert sind,
oder eines Salzes davon; oder

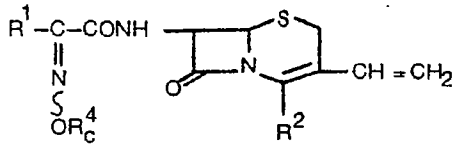
(8) Unterwerfen einer Verbindung der Formel



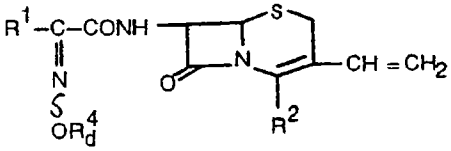
worin
R^2_b durch eine geschützte Amino- und eine geschützte Carboxygruppe substituiertes (C_1—C_7)Alkoxycarbonyl ist, und
R^1 und R^4 jeweils wie oben definiert sind,
oder eines Salzes davon der Entfernungsreaktion der Amino- und Carboxyschutzgruppe unter Bildung einer Verbindung der Formel



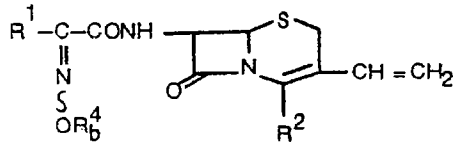
worin
R^2_c durch Amino und Carboxy substituiertes (C_1—C_7)Alkoxycarbonyl ist, und
R^1 und R^4 jeweils wie oben definiert sind,
oder eines Salzes davon; oder
(9) Unterwerfen einer Verbindung der Formel



worin
R^4_c durch eine geschüzte Amino- und eine geschützte Carboxygruppe substituiertes (C_1—C_7)Alkoxycarbonyl(C_1—C_7)alkyl oder durch eine geschützte Amino- und eine geschützte Carboxygruppe substituiertes (C_1—C_7)Alkyl ist, und
R^1 und R^2 jeweils wie oben definiert sind,
oder eines Salzes davon der Entfernungsreaktion der Amino- und Carboxyschutzgruppe unter Bildung einer Verbindung der Formel

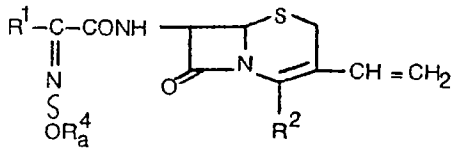


worin
R^4_d durch Amino und Carboxy substituiertes (C_1—C_7)Alkoxycarbonyl(C_1—C_7)alkyl oder durch Amino und Carboxy substituiertes (C_1—C_7)Alkyl ist, und
R^1 und R^2 jeweils wie oben definiert sind,
oder eines Salzes davon; oder
(10) Einführen einer Carboxyschutzgruppe oder einer Phosphonoschutzgruppe in eine Verbindung der Formel



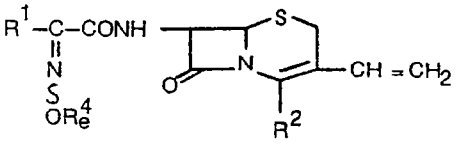
worin R^1, R^2 und R^4_b jeweils wie oben definiert sind,

oder ein Salz davon unter Bildung einer Verbindung der Formel



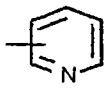
worin R^1, R^2 und R^4_a jeweils wie oben definiert sind, oder einer Salzes davon; oder

(11) Reagieren einer Verbindung der Formel



worin

R^4_e durch eine Gruppe der Formel



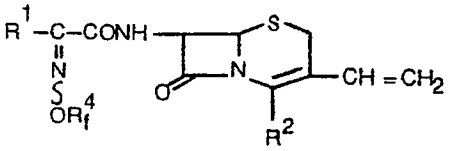
substituiertes (C_1—C_7)Alkyl ist, und

R^1 und R^2 jeweils wie oben definiert sind,

oder eines Salzes davon mit einer Verbindung der Formel

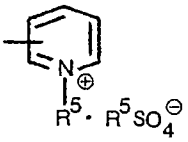
$$(R^5)_2SO_4$$

worin R_2 (C_1—C_7)Alkyl ist, unter Bildung einer Verbindung der Formel



worin

R^4_f durch eine Gruppe der Formel



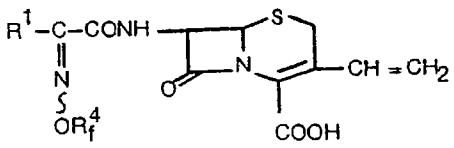
substituiertes (C_1—C_7)Alkyl ist, worin

R^5 wie oben definiert ist, und

R^1 und R^2 jeweils wie oben definiert sind,

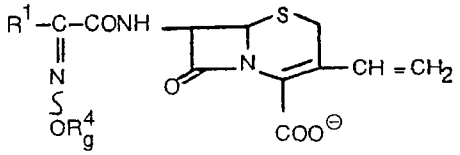
oder eines Salzes davon; oder

(12) Reagieren einer Verbindung der Formel

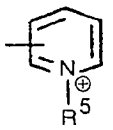


worin R^1 und R^4_f jeweils wie oben definiert sind,

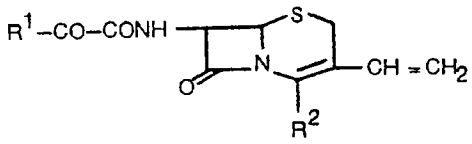
oder eines Salzes davon mit einer Base unter Bildung einer Verbindung der Formel



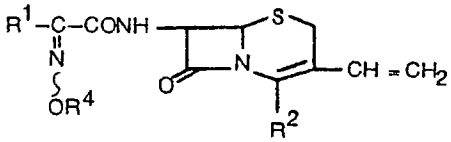
worin
R^4_g durch ein Kation der Formel



substituiertes (C_1—C_7)Alkyl ist, worin
R^5 wie oben definiert ist, und
R^1 wie oben definiert ist,
oder eines Salzes davon; oder
(13) Reagieren einer Verbindung der Formel



worin R^1 und R^2 jeweils wie oben definiert sind,
oder eines Salzes davon mit einer Verbindung der Formel R^4ONH_2, worin R^4 wie oben definiert ist, oder einem Salz davon unter Bildung einer Verbindung der Formel



worin R^1, R^2 und R^4 jeweils wie oben definiert sind,
oder eines Salzes davon.

2. Verfahren nach Anspruch 1, worin
R^1 Aminothiazolyl, welches Halogen aufweisen kann, Aminothiadiazolyl, Acylaminothiazolyl, welches Halogen aufweisen kann, Di(C_1—C_7)alkylaminomethylenaminothiadiazolyl ist,
R^4 Cyclo(C_3—C_7)alkenyl, (C_2—C_7)Alkinyl, (C_2—C_7)Alkenyl, durch Carboxy oder ein verestertes Carboxy substituiertes (C_2—C_7)Alkenyl, (C_1—C_7)Alkyl, durch einen oder zwei Substituenten, ausgewählt aus Carboxy, einer veresterten Carboxygruppe, Amino, Acylamino, Cyano, Phosphono, einer veresterten Phosphonogruppe und Pyridyl, substituiertes (C_1—C_7)Alkyl ist; und
R^2 Carboxy oder eine veresterte Carboxygruppe ist.

3. Verfahren nach Anspruch 2, welche das syn-Isomer hergestellt wird

4. Verfahren nach Anspruch 3, worin R^1 2-Aminothiazol-4-yl, 2-Amino-5-halogenthiazol-4-yl, 2-Aminothiazol-5-yl oder 5-Amino-1,2,4-thiadiazol-3-yl ist.

5. Verfahren nach Anspruch 4, worin R^4 Cyclo(C_3—C_7)alkenyl, (C_2—C_7)Alkinyl, (C_2—C_7)Alkenyl, Carboxy(C_2—C_7)alkenyl, verestertes Carboxy(C_2—C_7)alkenyl, (C_1—C_7)Alkyl, Carboxy(C_1—C_7)alkyl, verestertes Carboxy(C_1—C_7)alkyl, Amino- und Carboxy-substituiertes (C_1—C_7)Alkyl, Acylamino- und Estercarboxy-substituiertes (C_1—C_7)Alkyl, Cyano(C_1—C_7)alkyl, Phosphono(C_1—C_7)alkyl, verestertes Phosphono(C_1—C_7)alkyl oder Pyridyl(C_1—C_7)alkyl ist.

6. Verfahren nach Anspruch 5, worin R^2 Carboxy ist.

7. Verfahren nach Anspruch 6, worin R^4 Carboxy(C_1—C_7)alkyl ist.

8. Verfahren nach Anspruch 7, worin R^1 2-Aminothiazol-4-yl ist.

9. Verfahren nach Anspruch 8, in welchem 7-[2-(2-Aminothiazol-4-yl)-2-carboxymethoxyiminoacetamido]-3-vinyl-3-cephem-4-carbonsäure oder ihr Hydrochlorid oder ihr Dinatriumsalz hergestellt wird.

10. Verfahren nach Anspruch 8, in welchem Trihydrat von 7-[2-(2-Aminothiazol-4-yl)-2-carboxymethoxyiminoacetamido]-3-vinyl-3-cephem-4-carbonsäure hergestellt wird.

11. Verfahren nach Anspruch 6, in welchem R^1 2-Aminothiazol-4-yl ist und R^4 (C_1—C_7)Alkyl ist.

12. Verfahren nach Anspruch 11, in welchem 7-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-vinyl-3-cephem-4-carbonsäure oder ihr Natriumsalz hergestellt wird.

13. Verfahren nach Anspruch 5, in welchem R^2 Mono- oder Di- oder Triphenyl(C_1—C_7)alkoxycarbonyl, (C_1—C_7)Alkanoyloxy(C_1—C_7)alkoxycarbonyl, Amino- und Carboxy-substituiertes (C_1—C_7)Alkoxycarbonyl oder (C_1—C_7)Alkoxycarbonylamino- und Mono- oder Di- oder Triphenyl(C_1—C_7)alkoxycarbonyl-substituiertes (C_1—C_7)Alkoxycarbonyl ist.

14. Verfahren nach Anspruch 13, in welchem R^4 (C_1—C_7)Alkanoyloxy(C_1—C_7)alkoxycarbonyl-(C_1—C_7)alkyl oder (C_1—C_7)Alkoxycarbonyl(C_1—C_7)alkyl ist.

15. Verfahren nach Anspruch 14, in welchem R^1 2-Aminothiazol-4-yl ist.

16. Verfahren nach Anspruch 15, in welchem Pivaloyloxymethyl-7-[2-(2-aminothiazol-4-yl)-2-pivaloyloxymethoxycarbonylmethoxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylat hergestellt wird.

17. Verfahren nach Anspruch 13, in welchem R^1 2-Aminothiazol-4-yl ist und R^4 (C_1—C_7)Alkyl ist.

18. Verfahren nach Anspruch 17, in welchem Pivaloyloxymethyl-7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylat hergestellt wird.

19. Verfahren nach Anspruch 3, in welchem

7-[2-(2-Aminothiazol-4-yl)-2-{(1-methyl-3-pyridinio)-methoxyimino}acetamido]-3-vinyl-3-cephem-4-carboxylat oder ihr Hydrochlorid,

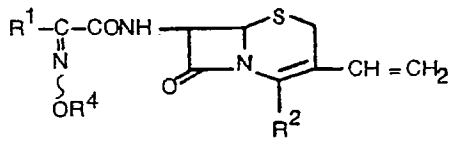
7-[2-(2-Aminothiazol-4-yl)-2-{(1-methyl-2-pyridinio)-methoxyimino}acetamido]-3-vinyl-3-cephem-4-carboxylat oder ihr Hydrochlorid,

1-Methyl-3-[1-(2-aminothiazol-4-yl)-1-{N-(4-benzhydryloxycarbonyl-3-vinyl-3-cephem-7-yl)-carbamoyl}methylenaminooxymethyl]-pyridinium-methylsulfat oder ihr Hydrochlorid, oder

1-Methyl-2-[1-(2-aminothiazol-4-yl)-1-{N-(4-benzhydryloxycarbonyl-3-vinyl-3-cephem-7-yl)carbamoyl}methylenaminooxymethyl]pyridinium-methylsulfat oder ihr Hydrochlorid hergestellt wird.

Revendications pour les Etats contractants: BE CH DE FR GB IT LI LU NL SE

1. Composé répondant à la formule:



dans laquelle

R^1 est un groupe aminothiazolyle qui peut porter un halogène, un groupe aminothiadiazolyle, un groupe aminothiazolyle protégé qui peut porter un halogène ou un groupe aminothiadiazolyle protégé;

R^2 est un groupe carboxy ou carboxy protégé, et

R^4 est l'hydrogène, un groupe cyclo(alcényle en C_3 à C_7), un groupe alcynyle en C_2 à C_7, un groupe alcényle en C_2 à C_7, un groupe alcényle en C_2 à C_7 substitué par un groupe carboxy ou carboxy protégé, un groupe alkyle en C_1 à C_7 ou un groupe alkyle en C_1 à C_7 substitué par un ou plusiers substituants choisis parmi un groupe carboxy, carboxy protégé, amino, amino protégé, cyano, phosphono, phosphono protégé et pyridyle

et un de ses sels pharmaceutiquement acceptables.

2. Composé selon la revendication 1, dans lequel

R^1 est un groupe aminothiazolyle qui peut porter un halogène, un groupe aminothiadiazolyle, un groupe acylaminothiazolyle qui peut porter un halogène, un groupe di(alkyle en C_1 à C_7)aminométhylèneaminothiadiazolyle,

R^4 est un groupe cyclo(alcényle en C_3 à C_7), alcynyle en C_2 à C_7, alcényle en C_2 à C_7, alcényle en C_2 à C_7 substitué par un groupe carboxy ou carboxy estérifié, un groupe alkyle en C_1 à C_7, un groupe alkyle en C_1 à C_7 substitué par un à deux substituants choisis parmi un groupe carboxy, carboxy estérifié, amino, acylamino, cyano, phosphono, phosphono estérifié et pyridyle; et

R^2 est un groupe carboxy ou un groupe carboxy estérifié.

3. Composé selon la revendication 2, qui est un isomère syn.

4. Composé selon la revendication 3, dans lequel R^1 est un groupe 2-aminothiazol-4-yle, 2-amino-5-halothiazol-4-yle, 2-aminothiazol-5-yle ou 5-amino-1,2,4-thiadiazol-3-yle.

5. Composé selon la revendication 4, dans lequel R^4 est un groupe cyclo(alcényle en C_3 à C_7), alcynyle en C_2 à C_7, alcényle en C_2 à C_7, carboxy(alcényle en C_2 à C_7), carboxy estérifié (alcényle en C_2 à C_7), alkyle en C_1 à C_7, carboxyl(alkyle en C_1 à C_7), carboxy estérifié(alkyle en C_1 à C_7), alkyle en C_1 à C_7 amino- et carboxy-substitué, un groupe alkyle en C_1 à C_7 substitué par un groupe acylamino et un groupe carboxy estérifié, un groupe cyano(alkyle en C_1 à C_7), phosphono(alkyle en C_1 à C_7), phosphono estérifié (alkyle en C_1 à C_7) ou pyridyl (alkyle en C_1 à C_7).

6. Composé selon la revendication 5, dans lequel R^2 est un groupe carboxy.

7. Composé selon la revendication 6, dans lequel R^4 est un groupe carboxy (alkyle en C_1 à C_7).

8. Composé selon la revendication 7, dans lequel R^1 est un groupe 2-aminothiazol-4-yle.

9. Composé selon la revendication 8, qui est l'acide 7-[2-(2-aminothiazol-4-yl)-2-carboxyméthoxyiminoacétamido]-3-vinyl-3-céphème-4-carboxylique ou son chlorhydrate ou son sel disodique.

10. Composé selon la revendication 8, qui est le trihydrate de l'acide 7-[2-(2-aminothiazol-4-yl)-2-carboxyméthoxyiminoacétamido]-3-vinyl-3-céphème-4-carboxylique.

11. Composé selon la revendication 6, dans lequel R^3 est un groupe 2-aminothiazol-4-yle et R^4 est un groupe alkyle en C_1 à C_7.

12. Composé selon la revendication 11, qui est l'acide 7-[2-(2-aminothiazol-4-yl)-2-méthoxyiminoacétamido]-3-vinyl-3-céphème-4-carboxylique ou son sel disodique.

13. Composé selon la revendication 5, dans lequel: R^2 est un groupe mono- ou di- ou triphényl(alcoxy en C_1 à C_7)carbonyle, (alcanoyle en C_1 à C_7) (alcoxy en C_1 à C_7)carbonyle, (alcoxy en C_1 à C_7)carbonyle amino- et carboxy-substitué, ou (alcoxy en C_1 à C_7)carbonyle substitué par un groupe (alcoxy en C_1 à C_7)carbonylamino et mono- ou di- ou tri-phényl(alcoxy en C_1 à C_7)carbonyle.

14. Composé selon la revendication 13, dans lequel: R^4 est une groupe (alcanoyloxy en C_1 à C_7) (alcoxy en C_1 à C_7)carbonyle(alkyle en C_1 à C_7) ou (alcoxy en C_1 à C_7)carbonyle(alkyle en C_1 à C_7).

15. Composé selon la revendication 14, dans lequel: R^1 est un groupe 2-aminothiazole-4-yle.

16. Composé selon la revendication 15, qui est le 7-[2-(2-aminothiazol-4-yl)-2-pivaloyloxyméthoxycarbonylméthoxyiminoacétamido]-3-vinyl-3-céphème-4-carboxylate de pivaloyloxyméthyle.

17. Composé selon la revendication 13, dans lequel: R^1 est un groupe 2-aminothiazol-4-yle et R^4 est un groupe alkyle en C_1 à C_7.

18. Composé selon la revendication 17, qui est le 7-[2-(2-aminothiazol-4-yl)-2-méthoxyiminoacétamido]-3-vinyl-3-céphème-4-carboxylate de pivaloyloxyméthyle.

19. Composé selon la revendication 3, qui est

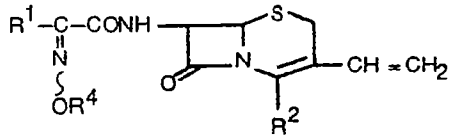
le 7-[2-(2-aminothiazol-4-yl)-2-{(1-méthyl-3-pyridinio)-méthoxyimino}acétamido]-3-vinyl-3-céphème-4-carboxylate ou son chlorhydrate,

le 7-[2-(2-aminothiazol-4-yl)-2-{(1-méthyl-2-pyridinio)-méthoxyimino}acétamido]-3-vinyl-3-céphème-4-carboxylate ou son chlorhydrate,

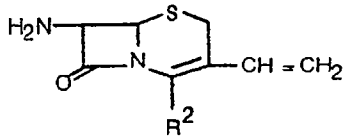
le méthylsulfate de 1-méthyl-3-[1-(2-aminothiazol-4-yl)-1-{N-(4-benzhydryloxycarbonyl-3-vinyl-3-céphème-7-yl)-carbamoyl}méthylèneaminooxyméthyl]pyridinium ou son chlorhydrate,

ou le méthylsulfate de 1-méthyl-2-[1-(2-aminothiazol-4-yl)-1-{N-(4-benzhydryloxycarbonyl-3-vinyl-3-céphème-7-yl)-carbamoyl}méthylène-aminooxyméthyl]pyridinium ou son chlorhydrate.

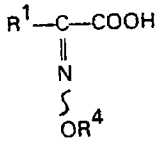
20. Procédé de préparation d'un composé répondant à la formule:



dans laquelle R^1, R^2 et R^4 sont tels que définis dans la revendication 1,
et un de ses sels pharmaceutiquement acceptables, qui consiste:
(1) à faire réagir un composé répondant à la formule:

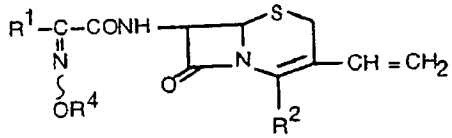


dans laquelle R^2 est tel que défini ci-dessus,
ou son dérivé réactif sur le groupe amino ou un de ses sels, avec un composé répondant à la formule:



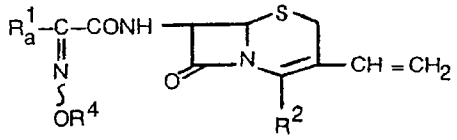
(III)

dans laquelle R^1 et R^4 sont chacun tels que définis ci-dessus, ou son dérivé réactif sur le groupe carboxy ou un de ses sels, pour donner un composé répondant à la formule:



dans laquelle R^1, R^2 et R^4 sont chacun tels que définis ci-dessus, ou un de ses sels;

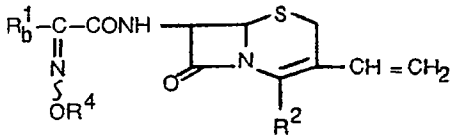
(2) à soumettre un composé répondant à la formule:



dans laquelle R_a^1 est un groupe aminothiazolyle protégé qui peut porter un halogène, ou un groupe aminothiadiazolyle protégé et

R^2 et R^4 sont chacun tels que définis ci-dessus,

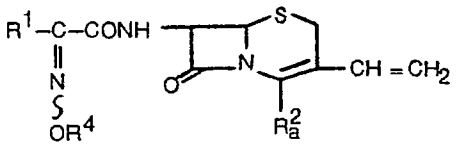
ou un de ses sels, à une réaction d'élimination du groupe protecteur du groupe amino pour donner un composé répondant à la formule:



dans laquelle R_b^1 est un groupe aminothiazolyle qui peut porter un halogène ou un groupe aminothiadiazolyle,

R^2 et R^4 sont chacun tels que définis ci-dessus ou un de ses sels, ou

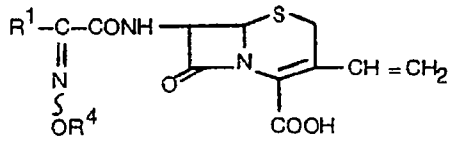
(3) à soumettre un composé répondant à la formule:



dans laquelle

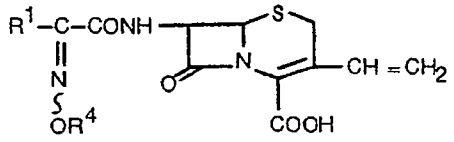
R_a^2 est un groupe carboxy protégé et

R^1 et R^4 sont chacun tels que définis ci-dessus, ou un de ses sels, à une réaction d'élimination du groupe protecteur du groupe carboxy, pour donner un composé répondant à la formule:

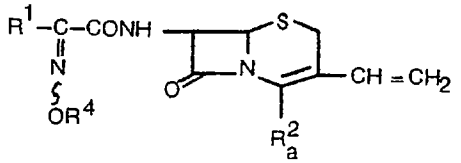


dans laquelle R^1 et R^4 sont chacun tels que définis ci-dessus, ou un de ses sels; ou

(4) à introduire un groupe protecteur du groupe carboxy dans un composé répondant à la formule:

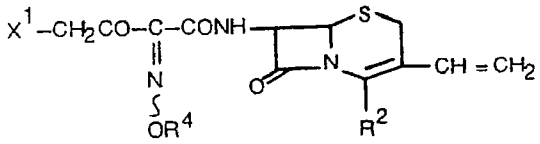


dans laquelle R^1 et R^4 sont chacun tels que définis ci-dessus, ou un de ses sels, pour donner un composé répondant à la formule:

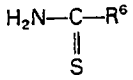


dans laquelle R^1, R_a^2 et R^4 sont chacun tels que définis ci-dessus, ou un de ses sels; ou

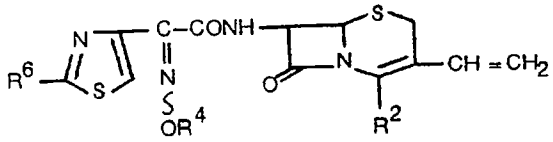
(5) à faire réagir un composé répondant à la formule:



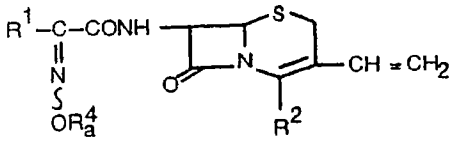
dans laquelle X^1 est un halogène, et
R^2 et R^4 sont chacun tels que définis ci-dessus,
ou un de ses sels, avec un composé répondant à la formule:



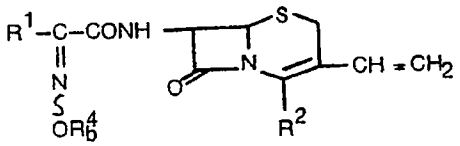
dans laquelle R^6 est un groupe amino ou amino protégé, pour donner un composé répondant à la formula:



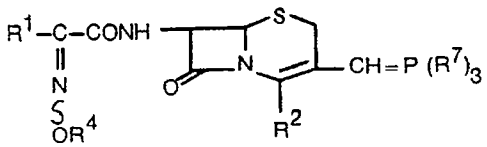
dans laquelle R^2, R^6 et R^4 sont chacun tels que définis ci-dessus, ou un de ses sels; ou
(6) à soumettre un composé répondant à la formule:



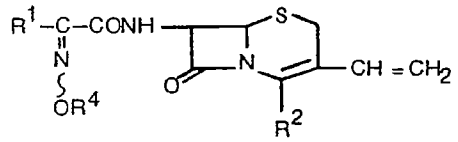
dans laquelle
R_a^4 est un groupe alkyle en C_1 à C_7 substitué par un groupe carboxy protégé ou un groupe phosphono protégé, ou un groupe alcényle en C_2 à C_7 substitué par un groupe carboxy protégé, et
R^1 et R^2 sont chacun tels que définis ci-dessus,
ou un de ses sels, à une réaction d'élimination du groupe protecteur du groupe carboxy ou du groupe protecteur du groupe phosphono pour donner un composé répondant à la formule:



dans laquelle
R_b^4 est un groupe alkyle en C_1 à C_7 substitué par un groupe carboxy ou phosphono, ou un groupe alcényle en C_2 à C_7 substitué par un groupe carboxy, et
R^1 et R^2 sont chacun tels que définis ci-dessus, ou un de ses sels; ou
(7) à faire réagir un composé répondant à la formule:

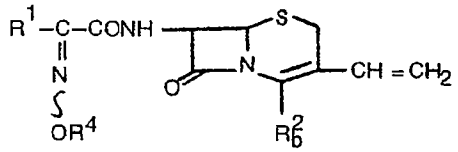


dans laquelle R^7 est un groupe aryle, et
R^1, R^2 et R^4 sont chacun tels que définis ci-dessus,
ou un de ses sels, avec du formaldéhyde, pour donner un composé répondant à la formule:



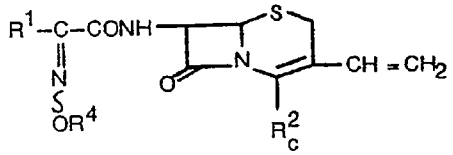
dans laquelle R^1, R^2 et R^4 sont chacun tels que définis ci-dessus,
ou un de ses sels; ou

(8) à soumettre un composé répondant à la formule:



dans laquelle R^2_b est un groupe (alcoxy en C_1 à C_7)carbonyle substitué par un groupe amino protégé et des groupes carboxy protégés et,

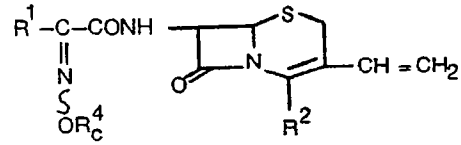
R^1 et R^4 sont chacun tels que définis ci-dessus,
ou un de ses sels, à une réaction d'élimination des groupes protecteurs des groupes amino- et carboxy- pour donner un composé répondant à la formule:



dans laquelle R^2_c est un groupe (alcoxy en C_1 à C_7)carbonyle substitué par des groupes amino et carboxy, et

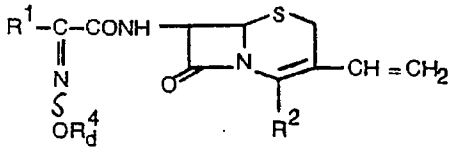
R^1 et R^4 sont chacun tels que définis ci-dessus,
ou un de ses sels; ou

(9) à soumettre un composé répondant à la formule:



dans laquelle R^4_c est un groupe (alcoxy en C_1 à C_7)carbonyle(alkyle en C_1 à C_7) substitué par un groupe amino protégé et par des groupes carboxy protégés, ou un groupe akyle en C_1 à C_7 substitué par un groupe amino protégé et par des groupes carboxy protégés, et

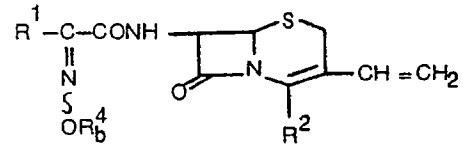
R^1 et R^2 sont chacun tels que définis ci-dessus, ou une de ses sels, à une réaction d'élimination des groupes protecteurs de l'amino- et du carboxy pour donner un composé répondant à la formule:



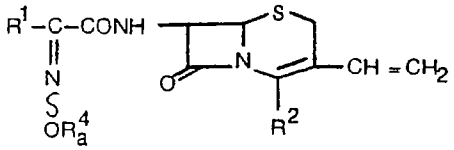
dans laquelle R^4_d est un groupe (alcoxy en C_1 à C_7)carbonyle(alkyle en C_1 à C_7) substitué par un groupe amino et un groupe carboxy, ou un groupe alkyle en C_1 à C_7 substitué par un groupe amino et un groupe carboxy, et

R^1 et R^2 sont chacun tels que définis ci-dessus, ou un de ses sels, ou

(10) à introduire un groupe protecteur du groupe carboxy ou un groupe protecteur du groupe phospono dans un composé répondant à la formule:

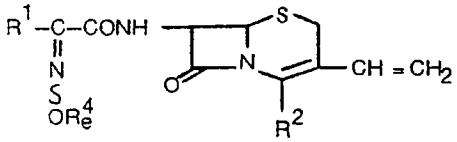


dans laquelle R^1, R^2 et R_b^4 sont chacun tels que définis ci-dessus, ou un de ses sels, pour donner un composé répondant à la formule:

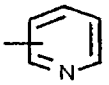


dans laquelle R^1, R^2 et R_a^4 sont chacun tels que définis ci-dessus, ou un de ses sels; ou

(11) à faire réagir un composé répondant à la formule:



dans laquelle R_e^4 est un groupe alkyle en C_1 à C_7 substitué par un groupe répondant à la formule:



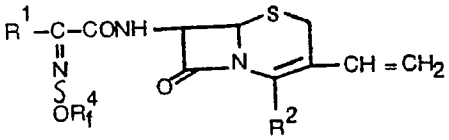
et

R^1 et R^2 sont chacun tels que définis ci-dessus,

ou un de ses sels avec un composé répondant à la formule:

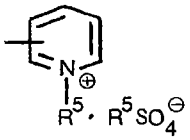
$$(R^5)_2SO_4$$

dans laquelle R^5 est un groupe alkyle en C_1 à C_7, pour donner un composé répondant à la formule:



dans laquelle

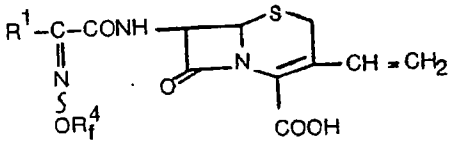
R_f^4 est un groupe alkyle en C_1 à C_7 substitué par un groupe répondant à la formule:



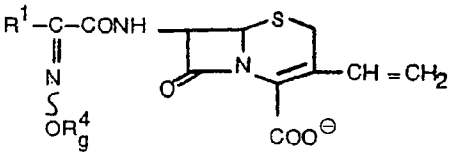
dans laquelle R^5 est tel que défini ci-dessus, et

R^1 et R^2 sont chacun tels que définis ci-dessus, ou un de ses sels, ou

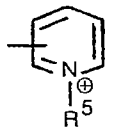
(12) à faire réagir un composé répondant à la formule:



dans laquelle R^1 et R_f^4 sont chacun tels que définis ci-dessus, ou un de ses sels, avec une base pour donner un composé répondant à la formule:

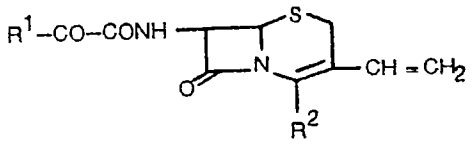


dans laquelle R_g^4 est un groupe alkyle en C_1 à C_7 substitué par un cation répondant à la formule:

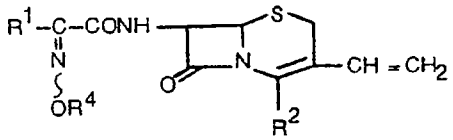


dans laquelle R^5 est tel que définis ci-dessus.

(13) à faire réagir un composé répondant à la formule:



dans laquelle R^1 et R^2 sont chacun tels que définis ci-dessus, ou un de ses sels, avec un composé répondant à la formule: R^4ONH_2, dans laquelle R_4 est tel que défini ci-dessus, ou un de ses sels, pour donner un composé répondant à la formule:



dans laquelle R^1, R^2 et R^4 sont chacun tels que définis ci-dessus,
ou un des ses sels.

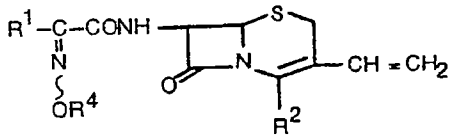
21. Composition pharmaceutique comprenant, comme ingrédients actifs, le composé revendiqué dans la revendication 1, en mélange avec des excipients pharmaceutiquement acceptables.

22. Composé selon l'une quelconque des revendications 1 à 19 pour l'utilisation dans le traitement de maladies infectieuses causées par des microorganismes pathogènes.

23. Utilisation d'un composé selon l'une quelconque des revendications 1 à 19, pour la préparation d'une composition pharmaceutique pour le traitement de maladies infectieuses causées par des microorganismes pathogènes.

Revendications pour l'Etat contractant: AT

1. Procédé de préparation d'un composé répondant à la formule:



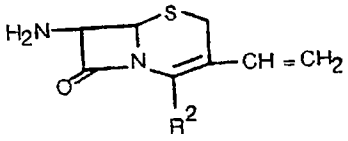
dans laquelle

R^1 est un groupe aminothiazolyle qui peut porter un halogène, un groupe aminothiadiazolyle, un groupe aminothiadiazolyle protégé qui peut porter un halogène ou un groupe aminothiadiazolyle protégé,

R^2 est un groupe carboxy ou carboxy protégé, et

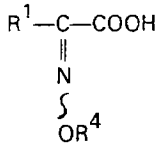
R^4 est l'hydrogène, un groupe cyclo(alcényle en C_3 à C_7), alcynyle en C_2 à C_7, alcényle en C_2 à C_7, alcényle en C_2 à C_7 substitué par un groupe carboxy ou carboxy protégé, alkyle en C_1 à C_7 ou alkyle en C_1 à C_7 substitué par un ou plusieurs substituants choisis parmi un groupe carboxy, carboxy protégé, amino, amino protégé, cyano, phosphono, phosphono protégé et pyridyle
et un de ses sels pharmaceutiquement acceptables,
qui consiste

(1) à faire réagir un composé répondant à la formule:



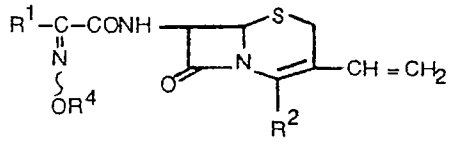
dans laquelle R^2 est tel que défini ci-dessus,

ou son dérivé réactif sur le groupe amino ou un de ses sels, avec un composé répondant à la formule:



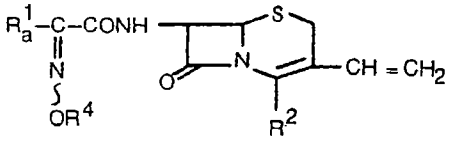
(III)

dans laquelle R^1 et R^4 sont chacun tels que définis ci-dessus, ou son dérivé réactif sur le groupe carboxy ou un de ses sels, pour donner un composé répondant à la formule:



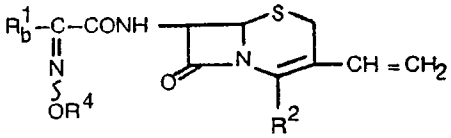
dans laquelle R^1, R^2 et R^4 sont chacun tels que définis ci-dessus, ou un de ses sels;

(2) à soumettre un composé répondant à la formule:



dans laquelle R_a^1 est un groupe aminothiazolyle protégé qui peut porter un halogène, ou un groupe aminothiadiazolyle protégé, et

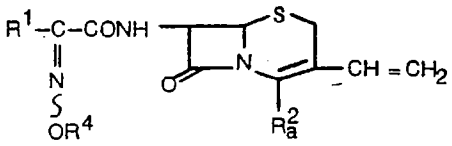
R^2 et R^4 sont chacun tels que définis ci-dessus ou un de ses sels, à une réaction d'élimination du groupe protecteur du groupe amino pour donner un composé répondant à la formule:



dans laquelle R_b^1 est un groupe aminothiazolyle qui peut porter un halogène ou un groupe aminothiadiazolyle, et

R^2 et R^4 sont chacun tels que définis ci-dessus, ou un de ses sels; ou

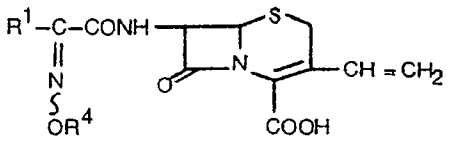
(3) à soumettre un composé répondant à la formule:



dans laquelle

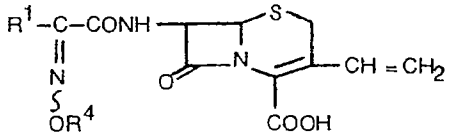
R_a^2 est un groupe carboxy protégé, et

R^1 et R^4 sont chacun tels que définis ci-dessus, ou un de ses sels, à une réaction d'élimination du groupe protecteur du groupe carboxy, pour donner un composé répondant à la formule:

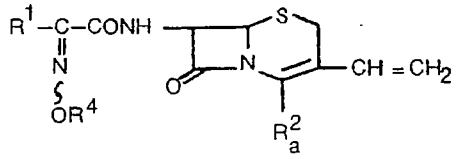


dans laquelle R^1 et R^4 sont chacun tels que définis ci-dessus, ou un de ses sels; ou

(4) à introduire un groupe protecteur du groupe carboxy dans un composé répondant à la formule:

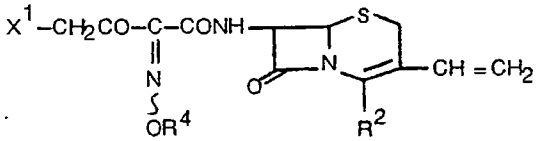


dans laquelle R^1 et R^4 sont chacun tels que définis ci-dessus,
ou un de ses sels, pour donner un composé répondant à la formule:

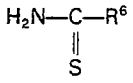


dans laquelle R^1, R^2_a et R^4 sont chacun tels que définis ci-dessus, ou un de ses sels; ou

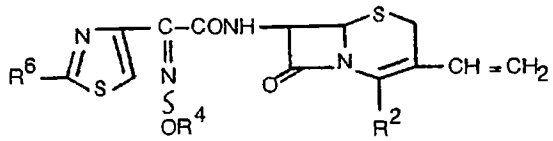
(5) à faire réagir un composé répondant à la formule:



dans laquelle X^1 est un halogène, et
R^2 et R^4 sont chacun tels que définis ci-dessus,
ou un de ses sels, avec un composé répondant à la formule:

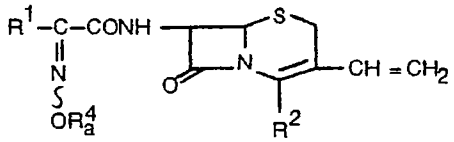


dans laquelle R^6 est un groupe amino ou amino protégé, pour donner un composé répondant à la formule:

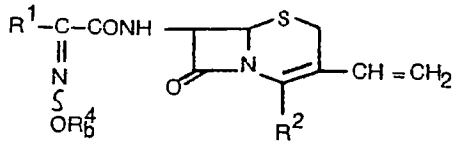


dans laquelle R^2, R^6 et R^4 sont chacun tels que définis ci-dessus, ou un de ses sels; ou

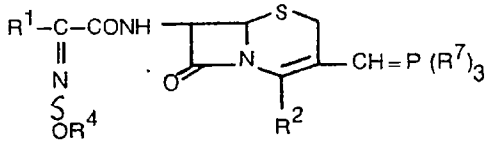
(6) à soumettre un composé répondant à la formule:



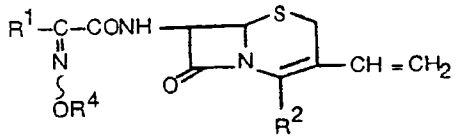
dans laquelle
R^4_a est un groupe alkyle en C_1 à C_7 substitué par un groupe carboxy protégé ou un groupe phosphono protégé, ou un groupe alcényle en C_2 à C_7 substitué par un groupe carboxy protégé, et
R^1 et R^2 sont chacun tels que définis ci-dessus,
ou un de ses sels, à une réaction d'élimination du groupe protecteur du groupe carboxy ou du groupe protecteur du groupe phosphono pour donner un composé répondant à la formule:



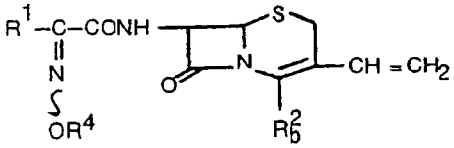
dans laquelle
R_b^4 est un groupe alkyle en C_1 à C_7 substitué par un groupe carboxy ou phosphono, ou un groupe alcényle en C_2 à C_7 substitué par un groupe carboxy, et
R^1 et R^2 sont chacun tels que définis ci-dessus,
ou un de ses sels; ou
(7) à faire réagir un composé répondant à la formule:



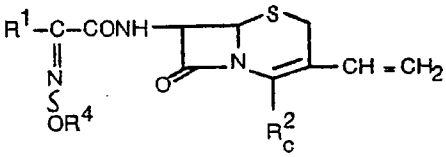
dans laquelle R^7 est un groupe aryle, et
R^1, R^2 et R^4 sont chacun tels que définis ci-dessus,
ou un de ses sels, avec le formaldéhyde, pour donner un composé répondant à la formule:



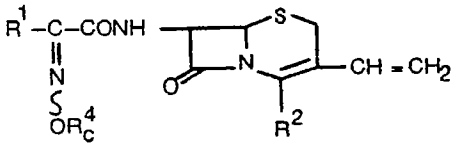
dans laquelle R^1, R^2 et R^4 sont chacun tels que définis ci-dessus,
ou un de ses sels; ou
(8) à soumettre un composé répondant à la formule:



dans laquelle R_b^2 est un groupe (alcoxy en C_1 à C_7)carbonyle substitué par un groupe amino protégé et par des groupes carboxy protégés et,
R^1 et R^4 sont chacun tels que définis ci-dessus,
ou un de ses sels, à une réaction d'élimination des groupes protecteurs des groupes amino- et carboxy- pour donner un composé répondant à la formule:

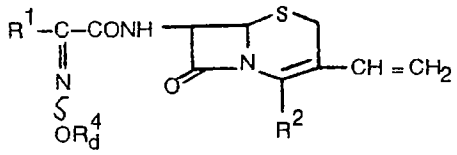


dans laquelle R_c^2 est un groupe (alcoxy en C_1 à C_7)carbonyle substitué par un groupe amino et un groupe carboxy, et
R^1 et R^4 sont chacun tels que définis ci-dessus,
ou un de ses sels; ou
(9) à soumettre un composé répondant à la formule:



dans laquelle
R_c^4 est un groupe (alcoxy en C_1 à C_7)carbonyle (alkyle en C_1 à C_7) substitué par un groupe amino protégé et par des groupes carboxy protégés, ou un groupe alkyle en C_1 à C_7 substitué par un groupe amino protégé et par des groupes carboxy protégés, et
R^1 et R^2 sont chacun tels que définis ci-dessus, ou un de ses sels, à une réaction d'élimination des

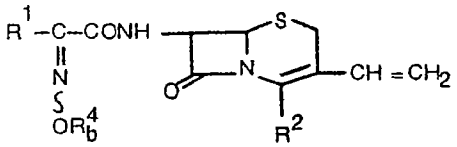
groupes protecteurs des groupes amino et des groupes carboxy, pour donner un composé répondant à la formule:



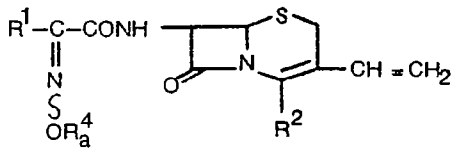
dans laquelle R_d^4 est un groupe (alcoxy en C_1 à C_7)carbonyle (alkyle en C_1 à C_7) substitué par un groupe amino et un groupe carboxy ou un groupe alkyle en C_1 à C_7 substitué par un groupe amino et un groupe carboxy, et

R^1 et R^2 sont chacun tels que définis ci-dessus, ou un de ses sels, ou

(10) à introduire un groupe protecteur du groupe carboxy ou un groupe protecteur du groupe phospono dans un composé répondant à la formule:

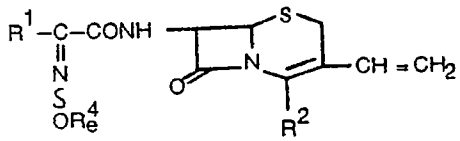


dans laquelle R^1, R^2 et R_b^4 sont chacun tels que définis ci-dessus, ou un de ses sels, pour donner un composé répondant à la formule:

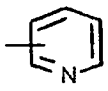


dans laquelle R^1, R^2 et R_a^4 sont chacun tels que définis ci-dessus, ou un de ses sels; ou

(11) à faire réagir un composé répondant à la formule:



dans laquelle R_e^4 est un groupe alkyle en C_1 à C_7 substitué par un groupe répondant à la formule:



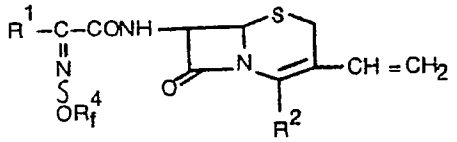
et

R^1 et R^2 sont chacun tels que définis ci-dessus,

ou un de ses sels avec un composé répondant à la formule:

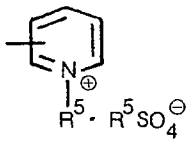
$$(R^5)_2SO_4$$

dans laquelle R^5 est un groupe alkyle en C_1 à C_7, pour donner un composé répondant à la formule:

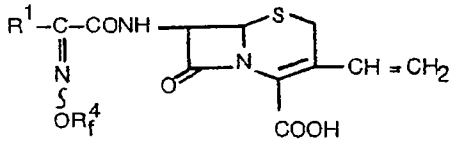


dans laquelle

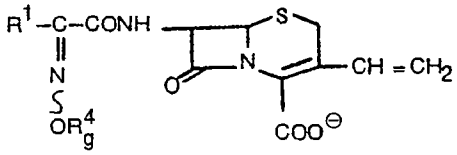
R_f^4 est un groupe alkyle en C_1 à C_7 substitué par un groupe répondant à la formule:



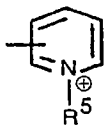
dans laquelle R^5 est tel que défini ci-dessus, et
R^1 et R^2 sont chacun tels que définis ci-dessus, ou un de ses sels; ou
(12) à faire réagir un composé répondant à la formule:



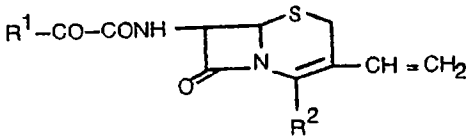
dans laquelle R^1 et R_f^4 sont chacun tels que définis ci-dessus, ou un de ses sels, avec une base pour donner un composé répondant à la formule:



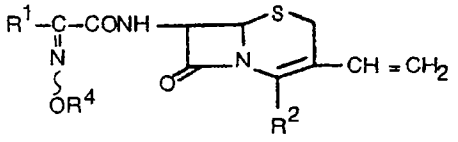
dans laquelle R_g^4 est un groupe alkyle en C_1 à C_7 substitué par un cation répondant à la formule:



dans laquelle R^5 est tel que défini ci-dessus, et
R^1 est tel que défini ci-dessus, ou un de ses sels; ou
(13) à faire réagir un composé répondant à la formule:



dans laquelle R^1 et R^2 sont chacun tels que définis ci-dessus, ou un de ses sels, avec un composé répondant à la formule: R^4ONH_2, dans laquelle R^4 est tel que défini ci-dessus, ou un de ses sels, pour donner un composé répondant à la formule:



dans laquelle R^1, R^2 et R^4 sont chacun tels que définis ci-dessus,
ou un de ses sels.

2. Procédé selon la revendication 1, dans lequel

R^1 est un groupe aminothiazolyle qui peut porter un halogène, un groupe aminothiadiazolyle, un groupe acylaminothiazolyle qui peut porter un halogène, un groupe di(alkylamino en C_1 à C_7)méthylène-aminothiadiazolyle,

R^4 est un groupe cyclo(alcényle en C_3 à C_7), alcynyle en C_2 à C_7, alcényle en C_2 à C_7, alcényle en C_2 à C_7 substitué par un groupe carboxy ou carboxy estérifié, un groupe alkyle en C_1 à C_7, alkyle en C_1 à C_7 substitué par un ou deux substituants choisis parmi les groupes carboxy, carboxy estérifié, amino, acylamino, cyano, phosphono, phosphono estérifié et pyridyle; et

R^2 est un groupe carboxy ou un groupe carboxy estérifié.

3. Procédé selon la revendication 2, dans lequel on prépare l'isomère syn.

4. Procédé selon la revendication 3, dans lequel R^1 est un groupe 2-aminothiazol-4-yle, 2-amino-5-halothiazol-4-yle, 2-aminothiazol-5-yle ou 5-amino-1,2,4-thiadiazol-3-yle.

5. Procédé selon la revendication 4, dans lequel R^4 est un groupe cycloalcényle en C_3 à C_7, alcynyle en C_2 à C_7, alcényle en C_2 à C_7, carboxy(alcényle en C_2 à C_7), carboxy estérifié (alcényle en C_2 à C_7), alkyle en C_2 à C_7, carboxy(alkyle en C_1 à C_7), carboxy estérifié(alkyle en C_1 à C_7), alkyle en C_1 à C_7 amino- et carboxy-substitué, alkyle en C_1 à C_7 substitué par un groupe acylamino et un groupe carboxy estérifié, cyano(alkyle en C_1 à C_7), phosphono(alkyle en C_1 à C_7), phosphono estérifié(alkyle en C_1 à C_7) ou pyridyle(alkyle en C_1 à C_7).

6. Procédé selon la revendication 5, dans lequel R^2 est un groupe carboxy.

7. Procédé selon la revendication 6, dans lequel R^4 est un groupe carboxy(alkyle en C_1 à C_7).

8. Procédé selon la revendication 7, dans lequel R^1 est un groupe 2-aminothiazol-4-yle.

9. Procédé selon la revendication 8, dans lequel on prépare l'acide 7-[2-(2-aminothiazol-4-yl)-2-carboxyméthoxyiminoacétamido]-3-vinyl-3-céphème-4-carboxylique ou son chlorhydrate ou son sel disodique.

10. Procédé selon la revendication 8, dans lequel on prépare le trihydrate de l'acide 7-[2-(2-aminothiazol-4-yl)-2-carboxyméthoxyiminoacétamido]-3-vinyl-3-céphème-4-carboxylique.

11. Procédé selon la revendication 6, dans lequel R^1 est un groupe 2-aminothiazol-4-yle et R^4 est un groupe alkyle en C_1 à C_7.

12. Procédé selon la revendication 11, dans lequel on prépare l'acide 7-[2-(2-aminothiazol-4-yl)-2-méthoxyiminoacétamido]-3-vinyl-3-céphème-4-carboxylique ou son sel disodique.

13. Procédé selon la revendication 5, dans lequel: R^2 est un groupe mono- ou di- ou triphényl(alcoxy en C_1 à C_7)carbonyle, (alcanoyloxy en C_1 à C_7) (alcoxy en C_1 à C_7)carbonyle, (alcoxy en C_1 à C_7)carbonyle, amino- et carboxy-substitué, ou (alcoxy en C_1 à C_7)carbonyle substitué par un groupe (alcoxy en C_1 à C_7)carbonylamino et mono- ou di- ou tri-substitué par un groupe phényl(alcoxy en C_1 à C_7)carbonyle.

14. Procédé selon la revendication 13, dans lequel: R^4 est un groupe (alcanoyloxy en C_1 à C_7) (alcoxy en C_1 à C_7)carbonyle(alkyle en C_1 à C_7) ou (alcoxy en C_1 à C_7)carbonyle (alkyle en C_1 à C_7).

15. Procédé selon la revendication 14, dans lequel:

R^1 est un groupe 2-aminothiazol-4-yle.

16. Procédé selon la revendication 15, dans lequel on prépare le 7-[2-(2-aminothiazol-4-yl)-2-pivaloyl-oxyméthoxycarbonylméthoxyimino-acétamido]-3-vinyl-3-céphème-4-carboxylate de pivaloyloxyméthyle.

17. Procédé selon la revendication 13, dans lequel:

R^1 est un groupe 2-aminothiazol-4-yle et

R^4 est un groupe alkyle en C_1 à C_7.

18. Procédé selon la revendication 17, dans lequel on prépare le 7-[2-(2-aminothiazol-4-yl)-2-méthoxy-iminoacétamido]-3-vinyl-3-céphème-4-carboxylate de pivaloyloxyméthyle.

19. Procédé selon la revendication 3, dans lequel on prépare

le 7-[2-(2-aminothiazol-4-yl)-2-{(1-méthyl-3-pyridino)-méthoxyimino}acétamido]-3-vinyl-3-céphème-4-carboxylate ou son chlorhydrate,

le 7-[2-(2-aminothiazol-4-yl)-2-{(1-méthyl-2-pyridino)-méthoxyimino}acétamido]-3-vinyl-3-céphème-4-carboxylate ou son chlorhydrate,

le méthylsulfate de 1-méthyl-3-[1-(2-aminothiazol-4-yl)-1-{N-(4-benzhydryloxycarbonyl-3-vinyl-3-céphème-7-yl)-carbamoyl}méthylèneaminooxyméthyl]pyridinium ou son chlorhydrate,

ou le méthylsulfate de 1-méthyl-2-[1-(2-aminothiazol-4-yl)-1-{N-(4-benzhydryloxycarbonyl-3-vinyl-3-céphème-7-yl)-carbamoyl}méthylène-aminooxyméthyl]pyridinium ou son chlorhydrate.